

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTH DAKOTA
EASTERN DIVISION**

THE RELIGIOUS SISTERS OF MERCY;
SACRED HEART MERCY HEALTH CARE
CENTER (Jackson, MN); SACRED HEART
MERCY HEALTH CARE CENTER (Alma,
MI); SMP HEALTH SYSTEM; UNIVER-
SITY OF MARY;

- and -

STATE OF NORTH DAKOTA,

Plaintiffs,

v.

SYLVIA BURWELL, Secretary
of the United States Department of
Health and Human Services; and UNITED
STATES DEPARTMENT OF HEALTH
AND HUMAN SERVICES,

Defendants.

No. 3:16-cv-00386-RRE-ARS

**Plaintiffs' Memorandum in
Support of Their Motion for
Preliminary Injunction**

TABLE OF CONTENTS

TABLE OF AUTHORITIES	iii
INTRODUCTION	1
STATEMENT OF FACTS	2
A. Title IX.....	2
B. Attempts to Add Protection for “Gender Identity”	3
C. The Affordable Care Act	3
D. Executive Branch Changes	3
E. The Rule.....	5
F. Plaintiffs and the Effect of the New Rule	7
ARGUMENT	11
I. The Rule violates the Administrative Procedure Act	12
A. HHS’s interpretation of “sex” to include “gender identity” is contrary to law.....	12
B. HHS’s failure to include religious or abortion- related exemptions is contrary to law, arbitrary and capricious, and in excess of statutory authority	18
1. The Rule is contrary to law, arbitrary and capricious, and exceeds statutory authority because it fails to include Title IX’s exemption for religious entities	18
2. The Rule is contrary to law, arbitrary and capricious, and exceeds statutory authority because it ignores Title IX’s abortion exemption	19
C. HHS’s failure to allow employers to accommodate employees’ religious beliefs is contrary to Title VII	20
II. The Rule violates the Religious Freedom Restoration Act	21

A. The Rule substantially burdens Plaintiffs’ religious exercise by imposing massive financial penalties 22

B. The Rule cannot satisfy strict scrutiny.....23

 1. The Rule furthers no compelling interest.....23

 2. Defendants have numerous less restrictive means of furthering their interests.....27

III. The Rule violates the Spending Clause 29

IV. The Rule violates the Free Speech Clause.....31

V. The Rule is unconstitutionally vague.....34

 A. The Rule fails to give fair notice of what conduct is subject to liability and gives HHS ample room for arbitrary enforcement.....35

 B. The Rule’s vague, overbroad, and content-based restrictions result in a serious chilling effect on protected expressive activity.....37

VI. A preliminary injunction is required.....38

CONCLUSION.....41

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>281 Care Comm. v. Arneson</i> , 766 F.3d 774 (8th Cir. 2014)	26, 40
<i>Agency for Int’l Dev. v. All. for Open Soc’y Int’l, Inc.</i> , 133 S. Ct. 2321 (2013).....	33
<i>Arlington Central School District Board of Education v. Murphy</i> , 548 U.S. 291 (2006).....	29
<i>Baggett v. Bullitt</i> , 377 U.S. 360 (1964).....	38
<i>Burwell v. Hobby Lobby Stores, Inc.</i> , 134 S. Ct. 2751 (2014).....	<i>passim</i>
<i>Cannon v. Univ. of Chicago</i> , 441 U.S. 677 (1979).....	2, 15
<i>Chalenor v. Univ. of N.D.</i> , 291 F.3d 1042 (8th Cir. 2002)	2, 16
<i>Christian Legal Soc’y v. Walker</i> , 453 F.3d 853 (7th Cir. 2006)	40
<i>Church of the Lukumi Babalu Aye, Inc. v. City of Hialeah</i> , 508 U.S. 520 (1993).....	23
<i>Conant v. Walters</i> , 309 F.3d 629 (9th Cir. 2002)	32
<i>Cramp v. Bd. of Pub. Instruction of Orange Cty., Fla.</i> , 368 U.S. 278 (1961).....	37
<i>Dept. of Health & Human Servs. v. CNS Int’l Ministries</i> , No. 15-775, 2016 WL 2842448 (U.S. May 16, 2016).....	11
<i>EEOC v. Abercrombie & Fitch Stores, Inc.</i> , 135 S. Ct. 2028 (2015).....	20
<i>Elrod v. Burns</i> , 427 U.S. 347 (1976).....	38

<i>Etsitty v. Utah Transit Auth.</i> , 502 F.3d 1215 (10th Cir. 2007)	13, 17
<i>F.C.C. v. Fox Television Stations, Inc.</i> , 132 S. Ct. 2307 (2012).....	34, 35, 37
<i>Gonzales v. O Centro Espirita Beneficente Uniao do Vegetal</i> , 546 U.S. 418 (2006).....	21, 33
<i>Grayned v. City of Rockford</i> , 408 U.S. 104 (1972).....	34, 37
<i>Gross v. Weber</i> , 186 F.3d 1089 (8th Cir. 1999)	29
<i>Hamilton v. Schriro</i> , 74 F.3d 1545 (8th Cir. 1996)	23
<i>Harris v. McRae</i> , 448 U.S. 297 (1980).....	26
<i>Hawkins v. Cmty. Bank of Raymore</i> , 761 F.3d 937 (8th Cir. 2014)	11-12
<i>Hobby Lobby Stores, Inc. v. Sebelius</i> , 723 F.3d 1114 (10th Cir. 2013)	38
<i>Holder v. Humanitarian Law Project</i> , 561 U.S. 1 (2010).....	34
<i>I.R.S., Fresno Serv. Ctr. v. FLRA</i> , 706 F.2d 1019 (9th Cir. 1983)	21
<i>Iowa Right to Life Comm., Inc. v. Williams</i> , 187 F.3d 963 (8th Cir. 1999)	38
<i>Johnston v. Univ. of Pittsburgh of Com. Sys. of Higher Educ.</i> , 97 F. Supp. 3d 657 (W.D. Pa. 2015).....	14
<i>Kansas v. United States</i> , 249 F.3d 1213 (10th Cir. 2001)	39
<i>Knox v. Serv. Emps. Int’l Union</i> , 132 S. Ct. 2277 (2012).....	30

<i>Korte v. Sebelius</i> , 735 F.3d 654 (7th Cir. 2013)	39
<i>N. Haven Bd. of Ed. v. Bell</i> , 456 U.S. 512 (1982).....	15
<i>New Motor Vehicle Bd. of California v. Orrin W. Fox Co.</i> , 434 U.S. 1345 (1977).....	39
<i>NFIB v. Sebelius</i> , 132 S. Ct. 2566 (2012).....	30
<i>Oglala Sioux Tribe of Indians v. Andrus</i> , 603 F.2d 707 (8th Cir. 1979)	21
<i>Opulent Life Church v. City of Holly Spring, Miss.</i> , 697 F.3d 279 (5th Cir. 2012)	39
<i>Pennhurst State Sch. & Hosp. v. Halderman</i> , 451 U.S. 1 (1981).....	28-29
<i>Premachandra v. Mitts</i> , 753 F.2d 635 (8th Cir. 1985)	29
<i>R.A.V. v. St. Paul</i> , 505 U.S. 377 (1992).....	33
<i>Rosenberger v. Rector</i> , 515 U.S. 819 (1995).....	33
<i>Sharpe Holdings, Inc. v. U.S. Dep’t of Health & Human Servs.</i> , 801 F.3d 927 (8th Cir. 2015)	<i>passim</i>
<i>Smith v. Goguen</i> , 415 U.S. 566 (1974).....	37, 38
<i>Sommers v. Budget Mktg., Inc.</i> , 667 F.2d 748 (8th Cir. 1982)	12, 13, 15, 16
<i>Sorrell v. IMS Health Inc.</i> , 564 U.S. 552 (2011).....	32
<i>South Dakota v. Dole</i> , 483 U.S. 203 (1987).....	28
<i>Sweet v. Mulberry Lutheran Home</i> , No. IP02-0320-C-H/K, 2003 WL 21525058 (S.D. Ind. June 17, 2003).....	14

<i>Texas v. E.P.A.</i> , 829 F.3d 405 (5th Cir. 2016)	39
<i>Texas v. United States</i> , 809 F.3d 134 (5th Cir. 2015)	40
<i>Texas v. United States</i> , No. 7:16-CV-00054-O, 2016 WL 4426495 (N.D. Tex. Aug. 21, 2016)	14, 30
<i>Ulane v. E. Airlines, Inc.</i> , 742 F.2d 1081 (7th Cir. 1984)	13, 17
<i>United States v. Smith</i> , 756 F.3d 1070 (8th Cir. 2014)	13
<i>United States v. Williams</i> , 553 U.S. 285 (2008)	34, 35
<i>Vill. of Hoffman Estates v. Flipside, Hoffman Estates, Inc.</i> , 455 U.S. 489 (1982)	37
<i>Walters v. Metro. Educ. Enters., Inc.</i> , 519 U.S. 202 (1997)	17
<i>Wolfe v. Fayetteville, Arkansas Sch. Dist.</i> , 648 F.3d 860 (8th Cir. 2011)	12
Statutes	
5 U.S.C. § 706	11
18 U.S.C. § 249	3, 16
20 U.S.C. § 1681	<i>passim</i>
20 U.S.C. § 1688	2, 19
42 U.S.C. § 1395	25
42 U.S.C. § 2000bb-1	21, 23
42 U.S.C. § 2000e	20
42 U.S.C. § 2000e-2	20
42 U.S.C. § 13925	3, 16
42 U.S.C. § 18023	26

42 U.S.C. § 18116.....	2, 3, 18, 20

Regulations

44 Fed. Reg. 71413 (Dec. 11, 1979)	3, 15
77 Fed. Reg. 5662 (Feb. 3, 2012)	4
81 Fed. Reg. 31376 (May 18, 2016)	<i>passim</i>
34 C.F.R. pt. 106.....	3
45 C.F.R. § 92.4.....	<i>passim</i>
45 C.F.R. § 92.101	2, 6, 12, 18
45 C.F.R. § 92.207	7
45 C.F.R. § 92.301	7, 22, 39
Exec. Order No. 13,672, 79 Fed. Reg. 42971 (July 21, 2014).....	5

Legislative Materials

118 Cong. Rec. 5808 (1972)	15
H.R. 166, 94th Cong. (1975).....	16
H.R. 1652, 113th Cong. (2013).....	3, 16
H.R. 2015, 110th Cong. (2007).....	3, 16
H.R. 2074, 96th Cong. (1979).....	16
H.R. 2981, 111th Cong. (2009).....	3, 16
H.R. 3185, 114th Cong. (2015).....	3, 16
H.R. 4636, 103rd Cong. (1994)	16
H.R. 14752, 93rd Cong. (1974)	16
Health Care and Education Reconciliation Act, Pub. L. 111-152 (March 30, 2010)	3
Patient Protection and Affordable Care Act, Pub. L. 111-148 (March 23, 2010)	3

S. 1858, 114th Cong. (2015).....	3, 16
S. 2081, 96th Cong. (1979).....	16
S. 439, 114th Cong. (2015).....	3, 16
S. 811, 112th Cong. (2011).....	3, 16
Social Security Amendments of 1965, Pub. L. No. 89–97, 79 Stat. 286.....	29

Other Authorities

American Heritage Dictionary (1976)	2, 14
Catherine E. Lhamon, Assistant Sec’y for Civil Rights, U.S. Dep’t of Educ., Office for Civil Rights, <i>Questions and Answers on Title IX and Sexual Violence</i> (2014).....	4
Compl., <i>Prescott v. Rady Children’s Hosp. - San Diego</i> , No. 16-2408 (S.D. Cal. Sept. 26, 2016).....	31
David Haig, <i>The Inexorable Rise of Gender and the Decline of Sex: Social Change in Academic Titles, 1945–2001</i> , Archives of Sexual Behav., Apr. 2004	14
Dear Colleague Letter on Harassment and Bullying from Russlynn Ali, Assistant Sec’y for Civil Rights, U.S. Dep’t of Educ., Office for Civil Rights (Oct. 26, 2010)	4
Def.’s Post-Trial Br., <i>Schroer v. Billington</i> , 577 F. Supp. 2d 293 (D.D.C. 2008) (No. 05-01090)	4, 17
Institute of Medicine of the National Academies, <i>The Health of Lesbian, Gay, Bisexual and Transgender People: Building a Foundation for Better Understanding</i> (2011).....	25
Joanne Meyerowitz, <i>A History of “Gender,”</i> 113 Am. Hist. Rev. 1346 (2008).....	14
Lena H. Sun & Lenny Bernstein, <i>U.S. Moves to Protect Women, Transgender People in Health Care</i> , Washington Post, Sep. 3, 2015	17
Letter from Jocelyn Samuels, Dir., Office for Civil Rights, Dep’t of Health & Human Servs., to Catherine W. Short, et al. (June 21, 2016).....	20

Mem. from the Attorney General on Treatment of Transgender
Employment Discrimination Claims Under Title VII of the
Civil Rights Act of 1964 (Dec. 15, 2014).....5

New Oxford American Dictionary (3d ed. 2010) 14

Oxford English Dictionary (1961) 14

Patricia A. Shiu, Director, U.S. Dep’t of Labor, Office of Fed.
Contract Compliance Programs, Directive 2014-02, Gender
Identity and Sex Discrimination (2014).....5

Press Release, Shantae Goodloe, U.S. Dep’t of Hous. and Urban Dev.,
HUD No. 10-139, *HUD Issues Guidance on LGBT Housing
Discrimination Complaints* (July 1, 2010),.....4

Sacred Heart Mercy Health Care Center, *Mission*,
<http://www.sacredheartmercy.org/mission/> 8

SMP Health System, *Philosophy*,
<http://www.smphs.org/mission-values-vision-philosophy.html> 8

Trans Health Clinics, Trans-Health.com,
<http://www.trans-health.com/clinics/> 28

U.S. Dep’t of Justice and U.S. Dep’t of Educ., Dear Colleague Letter
on Transgender Students, May 13, 2016 5

Webster’s Third New Int’l Dictionary (1971) 14

INTRODUCTION

In 45 days, Plaintiffs will run afoul of a new Rule issued by the Department of Health and Human Services that seeks to override the medical judgment of healthcare professionals across the country. On pain of massive liability, the Rule forces doctors and hospitals to perform controversial and potentially harmful medical procedures that purport to permanently alter an individual's sex—even when doing so would violate a doctor's religious beliefs and medical judgment, and even when the government's own programs exclude the procedures as potentially harmful.

The purported authority for this dramatic new mandate is the administrative redefinition of a single word in Title IX: “sex.” For decades, Congress has consistently used “sex” to refer to an individual's status as male or female, as determined by biological sex at birth. But in the new Rule, HHS redefines “sex” to include an individual's “gender identity,” which it defines as “an individual's internal sense of gender, which may be male, female, neither, or a combination of male and female, and which may be different from an individual's sex assigned at birth.” 45 C.F.R. § 92.4. HHS then claims that it is “discrimination” on the basis of “sex” to decline to perform gender transition procedures. Thus, with a single stroke of the pen, HHS has created massive new liability for thousands of doctors unless they cast aside their convictions and perform procedures that can be deeply harmful to their patients. It has also threatened to deprive the nation's most vulnerable citizens of healthcare by stripping states and hospitals of Medicare and Medicaid funds.

The Rule ought to be short-lived, because it cannot withstand even the slightest judicial scrutiny. HHS's attempt to redefine “sex” violates the Administrative Procedure Act. Its attempt to force doctors to violate their religious beliefs violates the Religious Freedom Restoration Act. Its attempt to manipulate the States violates the Spending Clause. And its attempt to control doctors' speech violates the Free Speech Clause. Accordingly, it must be enjoined.

STATEMENT OF FACTS

The Rule at issue here prohibits discrimination on the basis of “sex” in certain health activities. 45 C.F.R. § 92.101(a)(1). It defines “sex” to include, among other things, “gender identity.” *Id.* § 92.4. The purported authority for the Rule is Section 1557 of the Affordable Care Act (“ACA”), which prohibits discrimination in various health activities “on the ground prohibited under . . . title IX of the Education Amendments of 1972.” 42 U.S.C. § 18116(a). Title IX, in turn, prohibits discrimination in education on the basis of “sex.” 20 U.S.C. § 1681(a). Because the purported authority for the Rule ultimately comes from Title IX, we begin there.

A. Title IX

Congress enacted Title IX in 1972, prohibiting discrimination in certain education programs on the basis of “sex.” 20 U.S.C. § 1681(a). The statute expressly exempts religious organizations and precludes interpreting “sex” to mean abortion. 20 U.S.C. § 1681(a)(3); 20 U.S.C. § 1688.

At that time, the term “sex” was commonly understood to refer to the physiological differences between men and women, particularly with respect to reproductive functions. *See, e.g.*, American Heritage Dictionary 1187 (1976) (“The property or quality by which organisms are classified according to their reproductive functions.”). That understanding is reflected throughout the statute, which requires equal treatment with respect to two different “sexes”—male and female. *See, e.g.*, 20 U.S.C. § 1681(a)(8) (requiring comparable activities between students of “one sex” and “the other sex”). The law has long been interpreted to prohibit federally funded education programs from treating men better than women, or vice versa. *See, e.g.*, *Cannon v. Univ. of Chicago*, 441 U.S. 677, 680 (1979); *Chalenor v. Univ. of N.D.*, 291 F.3d 1042, 1044 (8th Cir. 2002).

B. Attempts to Add Protection for “Gender Identity”

Since Title IX was enacted, Congress has considered a variety of proposals to add new statutory protections based on “gender identity.” These include many attempts to amend both Title VII

and Title IX. *E.g.*, H.R. 2015, 110th Cong. (2007); H.R. 2981, 111th Cong. (2009); S. 811, 112th Cong. (2011); H.R. 1652, 113th Cong. (2013); S. 439, 114th Cong. (2015). And they include attempts currently pending in Congress to do precisely what the new Rule purports to do—prohibit discrimination in federally funded programs on the basis of “gender identity.” H.R. 3185, 114th Cong. (2015); S. 1858, 114th Cong. (2015). To date, almost all of these proposals have failed. But two have succeeded. First, in 2010, Congress enacted hate crimes legislation providing enhanced penalties for crimes motivated by “gender identity.” 18 U.S.C. § 249(a)(2). Second, in 2013, Congress reauthorized the Violence Against Women Act, prohibiting discrimination in certain funding programs on the basis of “sex” and—separately—“gender identity.” 42 U.S.C. § 13925(b)(13)(A).

C. The Affordable Care Act

Against this backdrop, in March 2010, Congress enacted the Patient Protection and Affordable Care Act, Pub. L. 111-148 (March 23, 2010), and the Health Care and Education Reconciliation Act, Pub. L. 111-152 (March 30, 2010), collectively known as the “Affordable Care Act” or “ACA.” As noted above, the key provision at issue in this case, Section 1557, does not use the term “sex” but instead prohibits discrimination “on the ground prohibited under . . . title IX of the Education Amendments of 1972 (20 U.S.C. 1681 et seq.).” 42 U.S.C. § 18116(a). Nothing in nearly 1,000 pages of text of the ACA mentions “gender identity.”

D. Executive Branch Changes

For several decades, across a variety of statutes, federal agencies consistently interpreted “sex” to refer to physiological differences between males and females. *See, e.g.*, A Policy Interpretation: Title IX & Intercollegiate Athletics, 44 Fed. Reg. 71413 (Dec. 11, 1979) (listing “male and female” 28 times, “men and women” 24 times, and “men’s and women’s” 21 times); Nondiscrimination on the Basis of Sex in Education Programs or Activities Receiving Federal Financial Assistance, 34 C.F.R. pt. 106 (addressing expenditures for male and female teams). As late as 2008, the U.S.

Department of Justice was still arguing that “the term ‘sex’ . . . prohibits discrimination based on the biological state of a male or female,” and that “a claim based on gender identity or transsexuality fails as outside the scope of [the term ‘sex’].” Def.’s Post-Trial Br. at 4, *Schroer v. Billington*, 577 F. Supp. 2d 293 (D.D.C. 2008) (No. 05-01090). No agency, to our knowledge, interpreted “sex” to include “gender identity” before 2010.

But in 2010, several months *after* enactment of the ACA, federal agencies issued a rash of letters, memos, executive orders, and regulations interpreting prohibitions on “sex” discrimination to include protections for “gender identity”:

- In July 2010, the Department of Housing and Urban Development (HUD) “announced a new policy . . . treat[ing] gender identity discrimination . . . as gender discrimination under the Fair Housing Act.”¹
- In October 2010, the Office for Civil Rights (OCR) for the Department of Education (DOE) issued a “Dear Colleague” letter asserting that, “[w]hen students are subjected to harassment on the basis of their LGBT status, they may also . . . be subjected to forms of sex discrimination prohibited under Title IX.”²
- In February 2012, HUD issued a regulation forbidding discrimination on the basis of “gender identity” in HUD-assisted or insured housing.³
- In April 2014, OCR issued a document stating that “Title IX’s sex discrimination prohibition extends to claims of discrimination based on gender identity . . .”⁴

¹ Press Release, Shantae Goodloe, U.S. Dep’t of Hous. and Urban Dev., HUD No. 10-139, *HUD Issues Guidance on LGBT Housing Discrimination Complaints* (July 1, 2010), http://portal.hud.gov/hudportal/HUD?src=/press/press_releases_media_advisories/2010/HUDNo.10-139.

² Dear Colleague Letter on Harassment and Bullying from Russlynn Ali, Assistant Sec’y for Civil Rights, U.S. Dep’t of Educ., Office for Civil Rights (Oct. 26, 2010), <http://www2.ed.gov/about/offices/list/ocr/letters/colleague-201010.pdf>.

³ Equal Access to Housing in HUD Programs Regardless of Sexual Orientation or Gender Identity, 77 Fed. Reg. 5662 (Feb. 3, 2012), <https://www.regulations.gov/contentStreamer?documentId=HUD-2011-0014-0312&disposition=attachment&contentType=pdf>.

⁴ Catherine E. Lhamon, Assistant Sec’y for Civil Rights, U.S. Dep’t of Educ., Office for Civil Rights, *Questions and Answers on Title IX and Sexual Violence* (2014), <http://www2.ed.gov/about/offices/list/ocr/docs/qa-201404-title-ix.pdf>.

- In July 2014, the President amended a 50-year-old executive order by adding “gender identity” to a list of prohibited bases of discrimination in federal contracting.⁵
- In August 2014, the Department of Labor issued a Directive that “discrimination based on gender identity or transgender status . . . is discrimination based on sex.”⁶
- In December 2014, the Department of Justice (DOJ) issued a memo concluding that Title VII’s reference to “sex” “encompasses discrimination based on gender identity, including transgender status.”⁷
- In May 2016, DOJ and DOE issued a “Dear Colleague Letter” stating that Title IX’s prohibition on “sex discrimination . . . encompasses discrimination based on a student’s gender identity.”⁸

None of these agency actions involved a statute that used the term “gender identity.”

E. The Rule

On May 18, 2016, after notice and comment, HHS issued the Rule at issue here—six years after Congress passed the ACA. The Rule applies to any “entity that operates a health program or activity, any part of which receives Federal financial assistance.” 45 C.F.R. § 92.4 (definition of “Covered entity”). “Federal financial assistance” is defined broadly to include “any grant, loan, credit, subsidy, contract . . . or any other arrangement” by which the federal government makes available its property or funds. *Id.* Thus, by HHS’s own estimate, the Rule applies to almost every health care provider in the country—including over 133,000 health care facilities (such as hospitals and health clinics) and “almost all licensed physicians”—because they all accept some form of

⁵ Exec. Order No. 13,672, 79 Fed. Reg. 42971 (July 21, 2014), <https://www.gpo.gov/fdsys/pkg/FR-2014-07-23/pdf/2014-17522.pdf>.

⁶ Patricia A. Shiu, Director, U.S. Dep’t of Labor, Office of Fed. Contract Compliance Programs, Directive 2014-02, Gender Identity and Sex Discrimination (2014), www.dol.gov/ofccp/regs/compliance/directives/dir2014_02.html.

⁷ Mem. from the Attorney General on Treatment of Transgender Employment Discrimination Claims Under Title VII of the Civil Rights Act of 1964 (Dec. 15, 2014) at 2, https://www.justice.gov/sites/default/files/opa/press-releases/attachments/2014/12/18/title_vii_memo.pdf.

⁸ U.S. Dep’t of Justice and U.S. Dep’t of Educ., Dear Colleague Letter on Transgender Students, May 13, 2016, <http://www2.ed.gov/about/offices/list/ocr/letters/colleague-201605-title-ix-transgender.pdf>.

federal funding, such as Medicare or Medicaid. Nondiscrimination in Health Programs and Activities, 81 Fed. Reg. 31376, 31445-46 (May 18, 2016).

The new Rule prohibits discrimination “on the basis of . . . sex,” defines “sex” to include “gender identity,” and defines “gender identity” as an individual’s “internal sense of gender, which may be male, female, neither, or a combination of male and female.” 45 C.F.R. § 92.101(a)(1), § 92.4. The Rule also defines “sex” to include discrimination based upon “termination of pregnancy.” 45 C.F.R. § 92.4.

Medical Procedures. The Rule requires covered entities to perform medical transition procedures or else be liable for “discrimination.” The Rule explains: “A provider specializing in gynecological services that previously declined to provide a medically necessary hysterectomy for a transgender man would have to revise its policy to provide the procedure for transgender individuals in the same manner it provides the procedure for other individuals.” 81 Fed. Reg. at 31455. In other words, if a gynecologist performs a hysterectomy for a woman with uterine cancer, she must do the same for a woman who wants to remove a healthy uterus to transition to living as a man. Thus, declining to remove a healthy organ is “discrimination.” HHS explains that this reasoning applies across the full “range of transition-related services.” *Id.* at 31435. This “is not limited to surgical treatments and may include, but is not limited to, services such as hormone therapy and psychotherapy, which may occur over the lifetime of the individual.” *Id.* at 31435-36.

In addition, because the new Rule prohibits discrimination on the basis of “termination of pregnancy,” it pressures healthcare providers who perform procedures such as a dilation and curettage for a miscarriage to perform the same procedure for an abortion.

Insurance Coverage. The Rule also requires covered entities to pay for medical transition

procedures in their health insurance plans. The Rule states: “A covered entity shall not, in providing or administering health-related insurance . . . [h]ave or implement a categorical coverage exclusion or limitation for all health services related to gender transition.” 45 C.F.R. § 92.207(b)(4). According to HHS, this means that a plan excluding “coverage for all health services related to gender transition is unlawful on its face.” 81 Fed. Reg. at 31429. In addition, if a doctor concludes that a hysterectomy “is medically necessary to treat gender dysphoria,” the patient’s employer would be required to cover that procedure on the same basis that it would cover a hysterectomy for other conditions (like cancer). *Id.* at 31429. Also, because the new Rule prohibits discrimination on the basis of “termination of pregnancy,” it pressures employers who cover procedures such as a dilation and curettage for a miscarriage to cover the same procedure for an abortion.

Enforcement. If a covered entity violates the Rule, it is subject to the same penalties that accompany a violation of Title IX. 45 C.F.R. § 92.301. These include the loss of federal funding (Medicare and Medicaid alone can total many millions of dollars), debarment from doing business with the government, and false claims liability. 81 Fed. Reg. at 31472; 45 C.F.R. § 92.301. Penalties also include enforcement proceedings brought by the Department of Justice, 81 Fed. Reg. at 31440, and private lawsuits for damages and attorneys’ fees. *Id.* at 31471; 45 C.F.R. § 92.301.

F. Plaintiffs and the Effect of the New Rule

The Plaintiffs are five private Catholic organizations and one State that will be adversely affected by the new Rule. Plaintiff **Religious Sisters of Mercy** is a Catholic order of religious sisters devoted to works of mercy, including offering healthcare to the underserved. Ex. A, ¶ 2 (Sister Mary Judith O’Brien Decl.). Each sister has chosen to follow Jesus Christ by taking a lifetime vow to serve the poor and sick by caring for the whole person—including physical, psychological, intellectual, and spiritual woundedness. *Id.* at ¶ 4. As part of their mission, they seek “to bring about that profound and extensive healing which is a continuation of the work of redemption.” Sacred

Heart Mercy Health Care Center, *Mission*, <http://www.sacredheartmercy.org/mission/> (last visited Nov. 16, 2016). Consistent with this mission, some of the sisters serve as licensed healthcare professionals in healthcare facilities throughout the country. Ex. A, ¶ 5-6 (Sister O'Brien Decl.).

The Religious Sisters of Mercy also own and operate two clinics that are Plaintiffs, both named **Sacred Heart Mercy Health Care Center**—one in Alma, Michigan, and one in Jackson, Minnesota. *Id.* at ¶ 6. Both are incorporated as religious nonprofits. *Id.* The clinics further the sisters' mission to care for the elderly and the poor by serving Medicare and Medicaid patients and by providing low-cost or free care to the uninsured. *Id.* at ¶ 8. Some of the sisters work in these clinics as doctors, nurses, or other healthcare professionals. *Id.* at ¶ 6. The clinics share the religious beliefs of the Religious Sisters of Mercy and are run in accordance with *The Ethical and Religious Directives of the United States Conference of Catholic Bishops*. *Id.*

Plaintiff **SMP Health System** is a non-profit Catholic health system headquartered in Fargo, North Dakota, and founded and sponsored by the Sisters of Mary of the Presentation. Ex. B, ¶ 3 (Sister Suzanne Stahl Decl.). The sisters believe that Catholic health care services and programs are ecclesial in nature, mandated by the Church to carry on the healing ministry of Jesus. SMP Health System, *Philosophy*, <http://www.smphs.org/mission-values-vision-philosophy.html> (last visited Nov. 16, 2016). As part of that healing ministry, SMP Health System provides a variety of health care services throughout North Dakota, including critical access hospitals, clinics, long-term care facilities, and senior housing. Ex. B, ¶ 3 (Sister Stahl Decl.). It has a special emphasis on providing services to the poor and elderly, including many Medicare and Medicaid patients. *Id.* at ¶ 4. SMP Health System shares the beliefs of the sisters and operates in accordance with *The Ethical and Religious Directives for Catholic Healthcare Services*. *Id.* at ¶ 5.

Plaintiff **University of Mary** is a Roman Catholic, Benedictine University with its main campus in Bismarck, North Dakota. The University infuses all of its programs with Christian, Catholic, Benedictine values to prepare its students to be ethical leaders in their communities. Ex. C, ¶ 6 (Monsignor James Patrick Shea Decl.). The University welcomes students of all faiths and backgrounds, and, as is fundamental to its mission, upholds Catholic teaching in all of its programs. *Id.* The University is subject to the Rule because it offers a nursing program that receives funding administered by HHS. *Id.* at ¶ 9. It also has a student health clinic. *Id.* at ¶ 11.

Like the Catholic Church they serve, these Plaintiffs believe that every man and woman is created in the image of God and reflects God's image in unique—and uniquely dignified—ways. Ex. A, ¶ 9 (Sister O'Brien Decl.); Ex B, ¶ 6 (Sister Stahl Decl.); Ex. C, ¶ 10 (Msgr. Shea Decl.). To the extent they provide medical services, Plaintiffs serve everyone in need, including transgender individuals. Ex. D, ¶ 6 (Sister Edith Mary Hart Decl.); Ex. E ¶ 4 (Dr. Richard Twanow Decl.). But they also believe that gender transition procedures are not in the best interests of their patients. Providing those procedures would violate their religious beliefs and medical judgment. Ex. D, ¶¶ 9-11 (Sister Hart Decl.); Ex. B, ¶ 8 (Sister Stahl Decl.); Ex. E, ¶ 5 (Dr. Twanow Decl.). They also have similar religious and medical objections to providing abortions or sterilizations. Ex. B, ¶¶ 9-10 (Sister Stahl Decl.); Ex. E, ¶¶ 8-9 (Dr. Twanow Decl.).

The Rule affects these Plaintiffs in two ways. First, the Rule requires Plaintiffs to offer medical services that violate their religious beliefs and medical judgment. Currently, Plaintiffs provide a variety of health services that are routinely requested as part of a gender transition. For example, the Sacred Heart Mercy Health Care Clinics provide endocrinology services and mental health counseling for anxiety and depression. Ex. D, ¶¶ 10-11 (Sister Hart Decl.). SMP Health System provides hysterectomies, mastectomies, endocrinology services, and psychiatric support. Ex. B,

¶ 8 (Sister Stahl Decl.). They willingly provide these services to everyone in need. Ex. D, ¶ 6 (Sister Hart Decl.). Ex. E, ¶ 4 (Dr. Twanow Decl.). But they cannot, in light of their religious beliefs and medical judgment, provide these services in furtherance of a gender transition. Ex. D, ¶¶ 9-11 (Sister Hart Decl.); Ex. B, ¶ 8 (Sister Stahl Decl.); Ex. E, ¶ 5 (Dr. Twanow Decl.). Under the new Rule, they are required “to revise [their] policy to provide the procedure for transgender individuals in the same manner [they] provide[] the procedure for other individuals,” or else they are liable for “discrimination” based on “gender identity.” 81 Fed. Reg. at 31455. If they do not comply, they are subject to the loss of federal funding, federal enforcement proceedings, and private lawsuits for damages and attorneys’ fees, which will cripple their religious mission to serve the poor.

Plaintiffs face a similar dilemma regarding abortion. Currently, Plaintiffs offer procedures for women who have miscarried a baby, such as dilation and curettage (D&C), that can also be used to perform an abortion. Ex. B, ¶ 10 (Sister Stahl Decl.). But they cannot offer these services in furtherance of an abortion. *Id.* Thus, under the Rule, they face the prospect of liability for “discrimination” based on “termination of pregnancy.” 45 C.F.R. § 92.4.

Second, the Rule requires Plaintiffs to provide insurance coverage for certain procedures in violation of their beliefs. As part of their religious beliefs, Plaintiffs provide health benefits to all of their eligible employees. Ex. A, ¶ 13 (Sister O’Brien Decl.); Ex. B, ¶ 11 (Sister Stahl Decl.); Ex. C, ¶ 12 (Msgr. Shea Decl.). But Plaintiffs cannot, in good conscience, include coverage in their insurance for abortions, sterilizations, or any drugs or procedures related to gender transition. Ex. A, ¶ 13 (Sister O’Brien Decl.); Ex. B, ¶ 11 (Sister Stahl Decl.); Ex. C, ¶ 14 (Msgr. Shea Decl.). Yet as of January 1, 2017, the Rule makes it “unlawful on its face” to adopt a “categorical” exclusion of “all health services related to gender transition.” 81 Fed. Reg. 31429. If they continue to

follow their conscience and medical judgment, these Plaintiffs face significant financial penalties.

Plaintiff **State of North Dakota** oversees and controls several agencies and a healthcare facility that receive federal funding administered by HHS. North Dakota also employs many healthcare professionals and provides health benefits to those employees and their families. The new Rule requires North Dakota to provide gender transition procedures, even when its doctors believe such procedures are harmful. If North Dakota's doctors have a religious objection to performing those procedures, the Rule makes it illegal for the State to accommodate those doctors' religious beliefs, even though Title VII would otherwise require it to do so. The Rule also compels North Dakota to provide insurance coverage for medical transition procedures and abortion procedures, as well as training, at significant financial cost. If North Dakota does not comply, it faces significant financial penalties, including loss of federal funding and private lawsuits for damages and attorneys' fees.

ARGUMENT

When determining whether to issue a preliminary injunction, the Court considers (1) the movant's likelihood of success on the merits, (2) the threat of irreparable harm to the movant, (3) the balance of harms between the parties, and (4) the public interest. *Sharpe Holdings, Inc. v. U.S. Dep't of Health & Human Servs.*, 801 F.3d 927, 936–37 (8th Cir. 2015), *vacated on other grounds*, *Dept. of Health & Human Servs. v. CNS Int'l Ministries*, No. 15-775, 2016 WL 2842448 (U.S. May 16, 2016). Because “the probability-of-success factor is the most significant,” *id.*, we begin there.

I. The Rule violates the Administrative Procedure Act.

Under the Administrative Procedure Act (“APA”), courts must “hold unlawful and set aside” agency actions that are “not in accordance with law” or “in excess of statutory jurisdiction, authority, or limitations, or short of statutory right.” 5 U.S.C. § 706(2)(A), (2)(C). APA claims proceed under “the two-step framework established by *Chevron*.” *Hawkins v. Cmty. Bank of Raymore*, 761

F.3d 937, 940 (8th Cir. 2014). First, courts use the “traditional tools of statutory construction” to interpret the statute. *Id.* If “the intent of Congress is clear as to the precise question at issue . . . that is the end of the matter.” *Id.* at 940. Second, and only if “the statute is silent or ambiguous,” the court considers whether the agency’s interpretation “defines a term in a reasonable way in light of the Legislature’s design.” *Id.* at 940-41 (internal quotation omitted). Here, the Rule conflicts with the unambiguous text of the statute, so it must be set aside at the first step.

A. HHS’s interpretation of “sex” to include “gender identity” is contrary to law.

The new Rule prohibits discrimination “on the basis of sex” in certain health activities, and defines “on the basis of sex” to include, among other things, “gender identity.” 45 C.F.R. § 92.101(a)(1), § 92.4. The purported authority for this Rule is Section 1557 of the ACA, which forbids federally funded health programs from discriminating “on the ground prohibited under” four other federal statutes: Title VI, 42 U.S.C. § 2000d (“race, color, or national origin”); Title IX, 20 U.S.C. § 1681 (“sex”); The Age Discrimination Act, 42 U.S.C. § 6101 (“age”); and the Rehabilitation Act, 29 U.S.C. § 794 (“disability”).

Section 1557 does not itself use the term “sex”; instead, it simply incorporates the prohibition contained in Title IX. Title IX’s key operative provision states:

No person in the United States shall, on the basis of sex, . . . be subjected to discrimination under any education program or activity receiving Federal financial assistance, except that . . . this section shall not apply to an educational institution which is controlled by a religious organization if the application of this subsection would not be consistent with the religious tenets of such organization.

20 U.S.C. § 1681(a)-(a)(3). Thus, a key question is whether “sex” in Title IX refers to physiological differences between males and females, or whether the term also means “gender identity.”

The Eighth Circuit has already answered this question in the analogous context of Title VII—which also prohibits discrimination on the basis of “sex”—and which the Eighth Circuit has held must be “treated interchangeably” with Title IX. *Wolfe v. Fayetteville, Arkansas Sch. Dist.*, 648

F.3d 860, 866 (8th Cir. 2011). Specifically, in *Sommers v. Budget Mktg., Inc.*, 667 F.2d 748 (8th Cir. 1982), the plaintiff alleged that her employment was terminated because of her gender identity—she was “transsexual”—and that this constituted discrimination on the basis of “sex” under Title VII. She argued that “the court should not be bound by the plain meaning of the term ‘sex’ under Title VII as connoting either male or female gender, but should instead expand the coverage of the Act to protect individuals such as herself who are psychologically female, albeit biologically male.” *Id.* at 749. The Eighth Circuit unanimously rejected her argument. Examining the text, purpose, and history of the Act, the Court held that “the word ‘sex’ in Title VII is to be given its traditional definition” (referring to “biological fact as the basis for determining sex”) “rather than an expansive interpretation.” *Id.* at 749-50. “Because Congress has not shown an intention to protect transsexuals, we hold that discrimination based on one’s transsexualism does not fall within the protective purview of the Act.” *Id.* at 750. *Sommers* thus fully resolves this case.

Sommers is also plainly correct. To determine the meaning of “sex,” the Court must examine the statute’s “text, structure, history, and purpose.” *United States v. Smith*, 756 F.3d 1070, 1075 (8th Cir. 2014), *cert. denied*, 135 S. Ct. 948 (2015). Here, as many courts have already held, the text, structure, history, and purpose of Title IX are clear: The word “sex” does not mean “gender identity.” *Sommers*, 667 F.2d at 750.⁹

⁹ See also, e.g.:

- *Etsitty v. Utah Transit Auth.*, 502 F.3d 1215, 1221 (10th Cir. 2007) (“This court agrees with . . . the vast majority of federal courts to have addressed this issue and concludes discrimination against a transsexual based on the person’s status as a transsexual is not discrimination because of sex”);
- *Ulane v. E. Airlines, Inc.*, 742 F.2d 1081, 1085 (7th Cir. 1984) (“The phrase in Title VII prohibiting discrimination based on sex, in its plain meaning, implies that it is unlawful to discriminate against women because they are women and against men because they are men. The words of Title VII do not outlaw discrimination against a person who has a sexual identity disorder.”);

Text. Because Title IX does not define “sex,” this Court must give the term its “ordinary, contemporary, common meaning.” *Smith*, 756 F.3d at 1073. When Title IX passed, virtually every dictionary definition of “sex” referred to physiological distinctions between females and males, particularly with respect to reproduction. *See, e.g.*, American Heritage Dictionary 1187 (1976); Webster’s Third New Int’l Dictionary 2081 (1971); 9 Oxford English Dictionary 578 (1961).

The term “gender identity,” by contrast, was rarely used. Until the 1950s, “gender” was used primarily by linguists to refer to grammatical classification. Joanne Meyerowitz, *A History of “Gender,”* 113 Am. Hist. Rev. 1346, 1353 (2008). But in the mid-1950s, psychologist John Money appropriated the term “gender” to refer to culturally determined roles for men and women, distinct from “biological sex.” *Id.* at 1354. Other social scientists adopted this new usage, and in 1963, Robert Stoller, a psychoanalyst, coined the term “gender identity.” David Haig, *The Inexorable Rise of Gender and the Decline of Sex: Social Change in Academic Titles, 1945–2001*, Archives of Sexual Behav., Apr. 2004, at 93. He argued that “sex was biological but gender was social.” *Id.* That usage was further popularized by feminist authors in the 1970s. Meyerowitz, *A History of “Gender,”* at 1353. Thus, to the extent “gender” or “gender identity” were used at the time of Title IX’s passage, they were used in *contrast* to “sex”: “gender” was socially constructed, “sex” was biological. That use remains common today. *See, e.g.*, New Oxford American Dictionary 721-22,

-
- *Texas v. United States*, No. 7:16-CV-00054-O, 2016 WL 4426495, at *14 (N.D. Tex. Aug. 21, 2016) (“[T]he plain meaning of the term sex” in Title IX regulations “meant the biological and anatomical differences between male and female students as determined at their birth.”);
 - *Johnston v. Univ. of Pittsburgh of Com. Sys. of Higher Educ.*, 97 F. Supp. 3d 657, 674 (W.D. Pa. 2015), appeal dismissed (Mar. 30, 2016) (“Title IX does not prohibit discrimination on the basis of transgender itself because transgender is not a protected characteristic under the statute.”);
 - *Sweet v. Mulberry Lutheran Home*, No. IP02-0320-C-H/K, 2003 WL 21525058, at *2 (S.D. Ind. June 17, 2003) (Hamilton, J.) (“[D]iscrimination on the basis of sex means discrimination on the basis of the plaintiff’s biological sex, not sexual orientation or sexual identity, including an intention to change sex.”).

1600 (3d ed. 2010) (“gender” is defined in social and cultural terms and “sex” in biological terms).

Purpose. This understanding of the term “sex” also fits Title IX’s purpose. Title IX was enacted based on Congressional hearings concerning pervasive discrimination against women in education. 44 Fed. Reg. at 71423; *N. Haven Bd. of Ed. v. Bell*, 456 U.S. 512, 523 n.13 (1982). Its chief sponsor said it was “an important first step in the effort to provide for the women of America something that is rightfully theirs—an equal chance to attend the schools of their choice” 118 Cong. Rec. 5808 (1972). Thus, the purpose of Title IX—like the purpose of banning sex discrimination in Title VII—was to “provid[e] equal opportunities for women.” *Sommers*, 667 F.2d at 750. There is no hint of any congressional purpose regarding “gender identity.”

Structure. This understanding of the term “sex” is also reflected throughout the statute, which requires equal treatment with respect to two different “sexes”—male and female. For example, the main operative section of Title IX states that if certain activities are provided for students of “one sex,” comparable activities must be provided for students of “the other sex.” 20 U.S.C. § 1681(a)(8). It also provides that schools may transition from admitting students of “only one sex” to admitting students of “both sexes.” *Id.* § 1681(a)(2). If, as HHS claims, the term “sex” includes an individual’s “internal sense of gender, which may be male, female, neither, or a combination of male and female,” 45 C.F.R. § 92.4, it makes no sense to refer to students of either “one sex” or “the other sex,” 20 U.S.C. § 1681(a)(8).

History. This understanding of “sex” is also consistent with Title IX’s history. “Gender identity” appears nowhere in Title IX’s legislative history. Rather, “[t]he legislative history of Title IX clearly shows that it was enacted because of discrimination that currently was being practiced against women in educational institutions.” 44 Fed. Reg. at 71423. That is also how courts have interpreted Title IX for decades. *See, e.g., N. Haven Bd. of Ed.*, 456 U.S. at 517-20; *Cannon*, 441

U.S. at 680; *Chalenor*, 291 F.3d at 1044.

More importantly, when Title IX was enacted, and ever since, Congress has treated “sex” and “gender identity” (along with “sexual orientation”) as distinct. In the 1970s, Congress rejected several proposals to amend the Civil Rights Act to add “sexual orientation.”¹⁰ Similarly, in 1994, Congress rejected the Employment Non-Discrimination Act (“ENDA”), which sought to prohibit employment discrimination on the basis of “sexual orientation.”¹¹ In 2007, 2009, and 2011, Congress rejected a broader version of ENDA, which, for the first time, sought to add protections for “gender identity.”¹² In 2013 and 2015, Congress rejected proposals to amend Title IX to add protections for “gender identity.”¹³ And Congress has so far rejected a proposal to do precisely what the new Rule purports to do—prohibit discrimination in federally funded programs on the basis of “gender identity.”¹⁴ None of these proposals makes any sense if Title IX and Title VII *already* prohibit such discrimination. *Sommers*, 667 F.2d at 750 (“Because Congress has not shown an intention to protect transsexuals, we hold that discrimination based on one’s transsexualism does not fall within the protective purview of the Act.”).

But not every proposal to protect “gender identity” failed. In 2010, Congress provided enhanced penalties for crimes motivated by “gender identity.” 18 U.S.C. § 249(a)(2). And in 2013, Congress prohibited discrimination in certain funding programs on the basis of both “sex” and “gender identity”—showing that Congress understands “sex” and “gender identity” to be distinct.

The same is true of federal agencies. For the first 38 years after Title IX’s enactment, federal

¹⁰ H.R. 14752, 93rd Cong. (1974); H.R. 166, 94th Cong. (1975); H.R. 2074, 96th Cong. (1979); S. 2081, 96th Cong. (1979).

¹¹ H.R. 4636, 103rd Cong. (1994).

¹² H.R. 2015, 110th Cong. (2007); H.R. 2981, 111th Cong. (2009); S. 811, 112th Cong. (2011).

¹³ H.R. 1652, 113th Cong. (2013); S. 439, 114th Cong. (2015).

¹⁴ H.R. 3185, 114th Cong. (2015); S. 1858, 114th Cong. (2015).

agencies issued numerous regulations, memos, and guidance documents interpreting Title IX. Those pronouncements uniformly reflected a definition of “sex” based on physiology. *See, e.g., supra* Statement of Facts, Part A. None mentioned “gender identity.” The Department of Justice also steadfastly maintained that “the term ‘sex’ . . . prohibits discrimination based on the biological state of a male or female,” and that “a claim based on gender identity or transsexuality fails as outside the scope of [the term ‘sex’].” Def.’s Post-Trial Br. at 4, *Schroer v. Billington*, 577 F. Supp. 2d 293 (D.D.C. 2008) (No. 05-01090). This uniform interpretation of “sex” by multiple federal agencies across several decades is further evidence of the term’s “ordinary, contemporary, common meaning.” *Walters v. Metro. Educ. Enters., Inc.*, 519 U.S. 202, 207 (1997) (citation omitted).

It was not until 2010 that federal agencies began issuing a rash of new pronouncements arguing that the term “sex” includes “gender identity.” *See supra* Statement of Facts, Part D. Not surprisingly, these pronouncements, including the Rule at issue here, were hailed as “groundbreaking.”¹⁵ But they were “groundbreaking” precisely because they redefined “sex.” And “groundbreaking” changes in the law are supposed to be made by the democratically-elected Congress, not unelected agencies. *See Etsitty*, 502 F.3d at 1222 (“If transsexuals are to receive legal protection apart from their status as male or female, however, such protection must come from Congress and not the courts.”); *Ulane*, 742 F.2d at 1086 (“If Congress believes that transsexuals should enjoy the protection of Title VII, it may so provide.”).

In short, the term “sex” is not ambiguous. It refers to the biological differences between males and females. HHS’s attempt to make it mean something different violates the APA.

¹⁵ *See, e.g.,* Lena H. Sun & Lenny Bernstein, *U.S. Moves to Protect Women, Transgender People in Health Care*, Washington Post, Sep. 3, 2015 (The new Rule “for the first time includes bans on gender identity discrimination as a form of sexual discrimination, language that advocacy groups have pushed for and immediately hailed as groundbreaking.”).

B. HHS’s failure to include religious or abortion-related exemptions is contrary to law, arbitrary and capricious, and in excess of statutory authority.

HHS’s Rule is also “contrary to law” and “in excess of statutory authority” because it contravenes the controlling statutes. Title IX, as incorporated by Section 1557, includes two exemptions relevant here: one for religious organizations, and one for abortion. Yet despite the fact that Section 1557 incorporated these exemptions, HHS refused to incorporate them in its Rule. This refusal is contrary to law and in excess of statutory jurisdiction and authority under the APA.

1. The Rule is contrary to law, arbitrary and capricious, and exceeds statutory authority because it fails to include Title IX’s exemption for religious entities.

Section 1557 prohibits discrimination “on the ground prohibited under . . . title IX of the Education Amendments of 1972.” 42 U.S.C. § 18116(a). Title IX’s prohibition on sex discrimination includes a broad exemption stating that Title IX “shall not apply to an educational institution which is controlled by a religious organization if the application of this subsection would not be consistent with the religious tenets of such organization.” 20 U.S.C. § 1681(a)(3). Thus when Congress incorporated “title IX of the Education Amendments of 1972” in Section 1557, it also included Title IX’s religious exemption. Yet despite many requests to include this exemption, HHS refused.

Notably, for other prohibited areas of discrimination—including race, color, national origin, age and disability—HHS complied with Congress’s incorporation of existing exceptions. *See* 45 C.F.R. § 92.101 (“The exceptions applicable to Title VI apply to discrimination on the basis of race, color, or national origin under this part. The exceptions applicable to Section 504 apply to discrimination on the basis of disability under this part. The exceptions applicable to the Age Act apply to discrimination on the basis of age under this part.”); *see also* 81 Fed. Reg. at 31378. But when it came to Title IX’s religious exemption, HHS parted ways with Congress. HHS stated that “certain protections already exist in Federal law with respect to religious beliefs,” and that HHS would rather make its own “determinations on a case-by-case basis, based on a thorough analysis

and relying on the extensive case law interpreting [other legal] standards.” *Id.* at 31379-80.

HHS also refused to apply Title IX’s religious exemption because it is “limited in scope to educational institutions.” *Id.* at 31380. But of course it is. *All of Title IX*—including its ban on sex discrimination—is limited to “educational institution[s].” 20 U.S.C. § 1681. When Congress brought the ban on sex discrimination into the healthcare context, it also brought the religious exemption. Both provisions are in the same section of the same statute, and both are expressly incorporated by Section 1557. HHS’s refusal to incorporate both is in excess of statutory authority.

2. The Rule is contrary to law, arbitrary and capricious, and exceeds statutory authority because it ignores Title IX’s abortion exemption.

The new Rule is equally dismissive of congressional intent on the issue of abortion. Title IX makes crystal clear that the ban on “sex” discrimination cannot be used as a means of requiring services or insurance coverage relating to abortion: “Nothing in this chapter shall be construed to require or prohibit any person, or public or private entity, to provide or pay for any benefit or service, including the use of facilities, related to an abortion.” 20 U.S.C. § 1688.

In its Proposed Rule, however, HHS did precisely what Congress forbade: it expanded the definition of sex discrimination to include discrimination on the basis of a “termination of pregnancy.” Understandably, several commenters expressed concern that this language might be read to require the provision of, or coverage or referral for, abortion. Again, however, HHS refused to abide by the limitations Congress included in Title IX. Instead, it simply noted the existence of *other* exemptions and conscience protections in federal law. 81 Fed. Reg. at 31380, 31388. HHS’s references to these statutory protections is cold comfort, given that HHS has interpreted some of

these protections very narrowly.¹⁶ More importantly, HHS’s refusal to follow the plain text of Title IX exceeds its statutory authority. Congress incorporated “title IX of the Education Amendments of 1972 (20 U.S.C. 1681 et seq.),” 42 U.S.C. § 18116(a)—which includes the abortion exemption—and it is not for the agency to cherry-pick which parts it will follow.

C. HHS’s failure to allow employers to accommodate employees’ religious beliefs is contrary to Title VII.

HHS’s Rule is also contrary to Title VII, because it makes it illegal for employers to accommodate the religious beliefs of their employees. North Dakota, for example, employs many healthcare workers, some of whom have religious objections to participating in medical transition procedures. Similarly, a number of the Religious Sisters of Mercy work for nonreligious healthcare employers. *See* Ex. A, ¶ 5 (Sister O’Brien Decl.); Ex. D, ¶ 3 (Sister Hart Decl.). Under Title VII, these employers are obligated to provide reasonable accommodations for their employees’ religious beliefs, as long as doing so does not impose an undue hardship on the employer. 42 U.S.C. §§ 2000e-2, 2000e(j); *EEOC v. Abercrombie & Fitch Stores, Inc.*, 135 S. Ct. 2028, 2032 (2015).

But the new Rule now makes these accommodations illegal. For example, the Rule says that if a doctor “works as an attending physician at a hospital,” then not just the doctor but also “[t]he hospital may be responsible for discrimination by the doctor’s practice that occurs at the hospital.” 81 Fed. Reg. at 31384 & n.40. The Rule also states that the hospital “will be held accountable for discrimination [by a doctor] under Section 1557” where “a doctor is an employee of a hospital.” *Id.* at 31384. Employers thus face an impossible choice: They must either force their doctors and

¹⁶ *See, e.g.*, Letter from Jocelyn Samuels, Dir., Office for Civil Rights, Dep’t of Health & Human Servs., to Catherine W. Short, et al. (June 21, 2016), <https://adflegal.blob.core.windows.net/web-content-dev/docs/default-source/documents/resources/media-resources/cdmhc-investigation-closure-letter.pdf?sfvrsn=2> (allowing California to require insurers to cover abortions over religious objections).

nurses to participate in gender transition procedures in violation of Title VII, or they must violate the new Rule. Because the new Rule conflicts with Title VII, it must be set aside under the APA.¹⁷

II. The Rule violates the Religious Freedom Restoration Act.

The new Rule also violates the Religious Freedom Restoration Act (“RFRA”). RFRA is a federal civil rights law that provides “very broad protection for religious liberty.” *Burwell v. Hobby Lobby Stores, Inc.*, 134 S. Ct. 2751, 2760 (2014). It provides that “Government may substantially burden a person’s exercise of religion only if it demonstrates that application of the burden to the person . . . is the least restrictive means of furthering [a] compelling governmental interest.” 42 U.S.C. § 2000bb-1(b)-(b)(2).

RFRA claims proceed in two steps. First, the Court must determine whether the government has imposed a “substantial burden” on the plaintiffs’ religious exercise. *Hobby Lobby*, 134 S. Ct. at 2775. Second, if a substantial burden exists, the government must satisfy strict scrutiny—that is, it must “‘demonstrate[] that application of the burden to the person’ represents the least restrictive means of advancing a compelling interest.” *Gonzales v. O Centro Espirita Beneficente Uniao do Vegetal*, 546 U.S. 418, 423 (2006) (citation omitted). Here, the Rule substantially burdens Plaintiffs’ religious exercise by requiring them, on pain of massive financial liability, to perform and pay for controversial medical procedures in violation of their religious beliefs. And the Rule does not even come close to satisfying strict scrutiny.

A. The Rule substantially burdens Plaintiffs’ religious exercise by imposing massive financial penalties.

Consistent with their religious beliefs, Plaintiffs are committed to caring for transgender individuals with compassion and respect. These Plaintiffs cannot, in accordance with their religious

¹⁷ See, e.g., *I.R.S., Fresno Serv. Ctr. v. FLRA*, 706 F.2d 1019, 1025 (9th Cir. 1983) (setting aside agency action that was inconsistent with Title VII); *Oglala Sioux Tribe of Indians v. Andrus*, 603 F.2d 707, 717 (8th Cir. 1979) (invalidating a regulation under one statute because it conflicted with another statute).

beliefs and medical judgment, participate in medical transition procedures. Ex. D, ¶¶ 9-11 (Sister Hart Decl.); Ex. B, ¶ 8 (Sister Stahl Decl.); Ex. E, ¶ 5 (Dr. Twanow Decl.). Nor can they participate in elective abortion or sterilization. Ex. B, ¶¶ 9-10 (Sister Stahl Decl.). Nor can they provide health benefits coverage for such procedures, or for sterilization or abortion, without violating their religious beliefs. Ex. A, ¶ 13 (Sister O’Brien Decl.); Ex. B, ¶ 11 (Sister Stahl Decl.); Ex. C, ¶ 14 (Msgr. Shea Decl.). But if Plaintiffs continue their religious exercise, they face massive financial penalties, including loss of Medicare, Medicaid, and other federal funds, 45 C.F.R. § 92.301; debarment from federal contracting; enforcement proceedings brought by the Department of Justice; liability under the False Claims Act, including treble damages, 81 Fed. Reg. at 31440; and private lawsuits brought by patients or employees for damages and attorneys’ fees, *id. id.* at 31472.

Financial penalties imposed on a religious practice are the quintessential example of a substantial burden. In *Hobby Lobby*, for example, the Court said that “[b]ecause the [Rule] forces [plaintiffs] to pay an enormous sum of money . . . if they insist on providing insurance coverage in accordance with their religious beliefs, the [Rule] clearly imposes a substantial burden on those beliefs.” *Hobby Lobby*, 134 S. Ct. at 2779. Similarly, in *Sharpe Holdings*, the Eight Circuit held that “[w]hen the government imposes a direct monetary penalty to coerce conduct that violates religious belief, ‘[t]here has never been a question’ that the government ‘imposes a substantial burden on the exercise of religion.’” 801 F.3d at 938 (citation omitted). This is an *a fortiori* case. The Rule imposes the same sort of enormous financial penalties, only this time, Plaintiffs are not only being forced to “provid[e] insurance coverage,” they are also being forced to perform the procedures that violate their religion. *Hobby Lobby*, 134 S. Ct. at 2779.

B. The Rule cannot satisfy strict scrutiny.

Because the Rule imposes a substantial burden on Plaintiffs’ religious exercise, the only re-

maining question is whether the Rule satisfies strict scrutiny. Strict scrutiny under RFRA is “exceptionally demanding.” *Sharpe Holdings*, 801 F.3d at 943 (quoting *Hobby Lobby*). Under that test, the government must demonstrate that the Rule furthers an interest “of the highest order.” *Church of the Lukumi Babalu Aye, Inc. v. City of Hialeah*, 508 U.S. 520, 546 (1993). And it “bear[s] the burden of demonstrating that the regulation is the least restrictive means of achieving a compelling interest.” *Hamilton v. Schrivo*, 74 F.3d 1545, 1552 (8th Cir. 1996) (citing 42 U.S.C. § 2000bb-1(b)). It cannot do so here.

1. The Rule furthers no compelling interest.

The government claims it has “a compelling interest in ensuring that individuals have nondiscriminatory access to health care and health coverage.” 81 Fed. Reg. at 31380. But under RFRA, such “[b]roadly formulated,’ or ‘sweeping’ governmental interests are inadequate.” *Sharpe Holdings*, 801 F.3d at 943 (citations omitted). Rather, RFRA requires courts “to ‘scrutiniz[e] the asserted harm of granting specific exemptions to particular religious claimants’—in other words, to look to the marginal interest in enforcing the [Rule] in [this case].” *Hobby Lobby*, 134 S. Ct. at 2779. The government has not done so here.

HHS asserts an interest in removing obstacles to access to healthcare for transgender individuals. 81 Fed. Reg. 31460. As discussed above, there is no indication that Congress shared this interest when it enacted Section 1557. *See supra* Part I.A & B. But in any case, the relevant question here is not whether Plaintiffs should offer healthcare services to transgender individuals. Plaintiffs are already willing to do so—for anything from cancer to the common cold. The question is whether the government has justified its “marginal interest” in forcing Plaintiffs to offer medical services and coverage for procedures that violate their best medical judgment and religious beliefs.

HHS cannot have a compelling interest in forcing private doctors to go against their own medical judgment and perform procedures that HHS’s own experts admit are potentially harmful. As

HHS’s medical experts wrote earlier this year: “Based on a thorough review of the clinical evidence available at this time, there is not *enough evidence to determine whether gender reassignment surgery improves health outcomes* for Medicare beneficiaries with gender dysphoria.”¹⁸ Instead, “There were conflicting (inconsistent) study results—of the best designed studies, some reported benefits while *others reported harms*.” *Id.* (emphasis added). For that reason, Medicare and Medicaid do not require coverage for gender reassignment surgery, but allow states and local administrators to make coverage determinations on a case-by-case basis.¹⁹ Many states forbid coverage entirely—with the full consent of HHS. This creates a bizarre situation—doctors are required under the Rule to perform and provide coverage for medical transition procedures because they accept Medicare and Medicaid, but Medicare and Medicaid often do not cover those procedures themselves because they are potentially harmful.

There are also sound medical reasons for not covering these procedures, particularly for children.²⁰ As guidance documents that HHS relied upon explain: “Gender dysphoria during childhood does not inevitably continue into adulthood. Rather, in follow-up studies of prepubertal children

¹⁸Ex. F (Centers for Medicare & Medicaid Services, *Proposed Decision Memo for Gender Dysphoria and Gender Reassignment Surgery* (June 2, 2016) <https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=282> (emphasis added) (“CMS Proposed Decision Memo”)).

¹⁹Ex. G (Centers for Medicare & Medicaid Services, *Decision Memo for Gender Dysphoria and Gender Reassignment Surgery* (Aug. 30, 2016), <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=282>).

²⁰ Jesse Singal, What’s Missing From the Conversation About Transgender Kids, NYMag.com: Science of Us, July 25, 2015, <http://nymag.com/scienceofus/2016/07/whats-missing-from-the-conversation-about-transgender-kids.html> (“[T]here is strong evidence that even many children with rather severe gender dysphoria will, in the long run, shed it and come to feel comfortable with the bodies they were born with.”).

(mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6-23% of children.”²¹ The same report noted that “Newer studies, also including girls, showed a 12-27% persistence rate of gender dysphoria” *Id.* Given that gender dysphoria will resolve in the overwhelming majority of children, the government cannot hope to prove that it has a compelling interest in requiring Plaintiffs to provide cross-sex hormones and other medical transition procedures for children.

Whether for children or adults, medical transition procedures also carry significant risks. The Institute of Medicine noted that transgender individuals “may be at increased risk for breast, ovarian, uterine, or prostate cancer as a result of hormone therapy.”²² The WPATH report notes that hormone therapy is associated with increased risk of cardiovascular disease, Type 2 diabetes, gallstones, venous thromboembolic disease, and hypertension. Ex. H at 40 (WPATH Report). This is a matter for careful consideration by doctors, not across-the-board rules, issued in a for-thee-but-not-for-me fashion, by political appointees in Washington. *Cf.* 42 U.S.C. § 1395 (“Nothing in this subchapter shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the practice of medicine or the manner in which medical services are provided.”).

With regard to abortions, Congress has long provided exemptions for medical professionals who cannot participate in abortion. The Rule itself notes that “the proposed rule would not displace

²¹ Ex. H at 11 (World Prof’l Ass’n for Transgender Health, *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, (7th ed. 2012), http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926 (footnote omitted) (WPATH Report) (cited in 81 Fed. Reg. at 31435 n.263)).

²² Institute of Medicine of the National Academies, *The Health of Lesbian, Gay, Bisexual and Transgender People: Building a Foundation for Better Understanding*, 264 (2011), http://www.beckett-fund.org/wp-content/uploads/2016/08/The-Health-of-LGBT-People_Book.pdf.

the protections afforded by provider conscience laws,” or “provisions in the ACA related to abortion services.” 81 Fed. Reg. at 31378, 31379. Therefore, the government has no compelling interest in forcing Plaintiffs to participate.

The government’s attempt to compel insurance coverage for medical transitions and abortion fails for similar reasons. As many courts have recognized, “A law cannot be regarded as protecting an interest of the highest order . . . when it leaves appreciable damage to that supposedly vital interest unprohibited.” *281 Care Comm. v. Arneson*, 766 F.3d 774, 785 (8th Cir. 2014), *cert. denied*, 135 S. Ct. 1550 (2015). Here, the government has exempted every employer in the country that does not receive certain federally administered funds. It has also exempted *its own insurance programs* from the Rule. As described above, Medicare and Medicaid are exempt. So is TRICARE, the military’s insurance program, which excludes coverage for “surgical treatment for gender dysphoria,” as well as cross-sex hormones and pubertal suppression for children under 16. TRICARE Policy Manual 6010.57-M, Chapter 7, Section 1.2 at 4.1, 3.2.3.1, 3.2.2.3 (updated: Sept. 6, 2016). And TRICARE protects the religious beliefs of physicians who object to performing gender transition procedures.²³ In short, the government seeks to impose on Plaintiffs a rule that has massive exemptions for others, including the government itself.

With regard to pregnancy termination, courts have long held that the right to an abortion does not include the right to an abortion at another’s expense. *See Harris v. McRae*, 448 U.S. 297 (1980) (upholding the Hyde Amendment, which restricts government funding for abortions). Congress ensured that insurers would not be required to cover abortions under the ACA. *See* 42

²³ Ex. I at 2-3 (Mem. from Karen S. Guice, Acting Assistant Sec’y of Def. to Assistant Sec’y of the Army, et al., Subject: Guidance for Treatment of Gender Dysphoria for Active and Reserve Component Service Members (July 29, 2016), http://www.defense.gov/Portals/1/features/2016/0616_policy/Guidance_for_Treatment_of_Gender_Dysphoria_Memo_FINAL_SIGNED.pdf (TRICARE Memo) (“In no circumstance will a provider be required to deliver care that he or she feels unprepared to provide either by lack of clinical skill or due to ethical, moral, or religious beliefs.”).

U.S.C. § 18023. The agency cannot now claim a compelling interest in doing the opposite.

2. Defendants have numerous less restrictive means of furthering their interests.

Even assuming the Rule furthered a compelling governmental interest—and it does not—the Rule also fails strict scrutiny because there are numerous less restrictive alternatives. Under RFRA, the government must “come forward with evidence that [its Rule is] the only feasible means to [accomplish its goal] and that no alternative means would suffice to achieve its compelling interest.” *Sharpe Holdings*, 801 F.3d at 943. But numerous alternatives are available here.

If the government wishes to increase access to gender transition services and insurance coverage for those services, “[t]he most straightforward way of doing this would be for the Government to assume the cost of providing the [procedures] at issue to any [individuals] who are unable to obtain them under their health-insurance policies due to their employers’ religious objections.” *Hobby Lobby*, 134 S. Ct. at 2780. For example, “the government could provide subsidies, reimbursements, tax credits, or tax deductions to employees” or “the government could pay for the distribution of [services] at community health centers, public clinics, and hospitals with income-based support.” *Sharpe Holdings*, 801 F.3d at 945. Here, as in *Hobby Lobby* and *Sharpe Holdings*, “the government has not shown that these alternatives are infeasible.” *Id.*

The government could also set up an alternative system for provision of benefits. Indeed, the government has already essentially done so: It requires insurance plans on its own exchanges to offer this coverage. 81 Fed. Reg. 31428. The government need not coerce religious charities when it has created its own marketplaces to offer this type of care to those who wish to obtain it. The government also offers credits to those who need help affording health care on the exchanges; those same credits could be made available to individuals who do not have this coverage through their employers. The government could also set up an alternative coverage mechanism, as it has done with the preventive services mandate. *See Hobby Lobby*, 134 S. Ct. at 2781-82. As in *Sharpe*

Holdings, “we cannot say on this limited record that the government has eliminated the use of [these alternatives] as a viable option.” 801 F.3d at 945.

The government also has many alternatives available besides coercing the participation of medical professionals. Many doctors and hospitals provide medical transition services; in fact, many hospitals have established centers of excellence for transgender procedures. *See, e.g., Trans Health Clinics*, Trans-Health.com, <http://www.trans-health.com/clinics/> (last updated Aug. 4, 2016) (listing “health clinics that specialize in trans health care”). If the government wants to increase access to gender transition services—and get better care for people who want them—the government could partner with willing professionals to increase access. It could train health care navigators to assist individuals in finding such services, just as it does with assisting individuals to find plans on the exchanges. Such options would not only increase access to health care for transgender individuals, they would focus upon doctors with special expertise in transgender issues, rather than conscripting unwilling doctors who may not have the necessary expertise.

III. The Rule violates the Spending Clause.

The Rule also violates the Spending Clause by imposing unauthorized and coercive conditions on the States. Congress is permitted to use its power under the Spending Clause to induce States to voluntarily accept federal conditions in exchange for the receipt of federal funds. But such conditions must be both (a) unambiguous and (b) non-coercive. *South Dakota v. Dole*, 483 U.S. 203, 207-08, 211 (1987). The Rule fails both tests.

First, the alleged condition on spending was hardly “unambiguous.” Congress never conditioned the States’ acceptance of Medicare and Medicaid funding on agreement with the agency’s new definition of “sex.” Congressional attempts to use the spending power to induce States to accept federal conditions “is much in the nature of a contract: in return for federal funds, the States agree to comply with federally imposed conditions.” *Pennhurst State Sch. & Hosp. v. Halderman*,

451 U.S. 1, 17 (1981). For this reason, “[t]he legitimacy of Congress’ power to legislate under the spending power thus rests on whether the State voluntarily and knowingly accepts the terms of the ‘contract.’” *Id.* Of course States cannot voluntarily and knowingly accept conditions they do not know about. “Accordingly, if Congress intends to impose a condition on the grant of federal monies, it must do so unambiguously.” *Id.*

Many courts have struck down or refused to impose ambiguous conditions on federal funds. For example, in *Gross v. Weber*, the Eighth Circuit refused to impose retroactive Title IX liability on a school district on the grounds that “[t]itle IX provides no notice that educational institutions will be subject to liability for prior events. It would be unfair to impose a greater duty than that which the educational institutions agreed to assume.” *Gross v. Weber*, 186 F.3d 1089, 1092 (8th Cir. 1999). Likewise, in *Pennhurst*, the Supreme Court found that Congress had failed to unambiguously require participating States to satisfy the statute’s “bill of rights” provisions in a program for the developmentally disabled. As the Court explained, “where Congress has intended the States to fund certain entitlements as a condition of receiving federal funds, it has proved capable of saying so explicitly.” *Id.* at 17–18. Since the “bill of rights” provisions were not imposed unambiguously, the Court concluded that the States could not be forced to comply. *See also Arlington Central School District Board of Education v. Murphy*, 548 U.S. 291, 297 (2006) (federal statute “does not even hint” at the condition imposed on state officials).

Here, there is no plausible argument that Congress unambiguously told the States that their receipt of Medicare and Medicaid funds was conditioned on embracing the agency’s newly-minted definition of “sex.” To understand the terms North Dakota accepted, “the focus must be on the law when [the relevant statute] was enacted.” *Premachandra v. Mitts*, 753 F.2d 635, 638 (8th Cir. 1985) (en banc). Both Medicaid and Medicare were adopted in 1965. Social Security Amendments

of 1965, Pub. L. No. 89–97, 79 Stat. 286. But there is nothing in either statute to suggest that states accepting government funds to care for the poor and elderly through these programs were “unambiguously” informed—or informed *at all*—that their participation in helping those in need also included an agreement to abide by the government’s interpretation of the word “sex” fifty years into the future. Indeed, as explained above, the agency’s interpretation of “sex” is not even consistent with Title IX. Rather, “the common understanding” of the term “sex” “when Title IX was enacted” referred to “the biological differences between male and female.” *Texas v. United States*, 2016 WL 4426495 at *15.

The Rule also violates the Spending Clause because it is unconstitutionally coercive. “Congress may use its spending power to create incentives for States to act in accordance with federal policies. But when “‘pressure turns to compulsion,’ the legislation runs contrary to our system of federalism.” *NFIB*, 132 S. Ct. at 2602 (citation omitted). In *NFIB*, the Supreme Court considered the line that separates appropriate spending conditions from the proverbial “gun to the head.” *Id.* at 2602-04. It held that a threat to eliminate all federal Medicaid funding, which constituted “10 percent of a State’s overall budget,” was unconstitutionally coercive. *Id.* at 2604-05. Here, North Dakota faces even more coercion than was rejected by seven justices in *NFIB*, because it stands to lose not only all of its Medicare funding, but all other HHS funding, and to face private lawsuits for damages and attorneys’ fees. Thus, this is an *a fortiori* case.

IV. The Rule violates the Free Speech Clause.

The Rule also violates the Free Speech Clause by prohibiting doctors from expressing some points of view and compelling them to express others. Under the First Amendment, “[t]he government may not prohibit the dissemination of ideas that it disfavors, nor compel the endorsement of ideas that it approves.” *Knox v. Serv. Emps. Int’l Union*, 132 S. Ct. 2277, 2288 (2012) (citations omitted). Here, the new Rule does both.

First, the Rule deems a particular medical viewpoint to be discriminatory—namely, the viewpoint that transition-related treatment is “experimental.” 81 Fed. Reg. at 31435; *see also id.* at 31429. HHS rejects this viewpoint as “outdated and not based on current standards of care” and approvingly cites another HHS document stating that “sex reassignment surgery *can no longer be considered* an experimental treatment.” *Id.* at 31435 & n.263 (citing Ex. J at 22-24 (U.S. Dep’t of Health & Human Servs., Departmental Appeals Bd., Appellate Division NCD 140.3, Docket No. A-13-87, Decision No. 2576 (May 30, 2014), <http://www.hhs.gov/sites/default/files/static/dab/decisions/board-decisions/2014/dab2576.pdf>)). Thus, if a covered entity advises a patient that a medical transition procedure is “experimental”—as Plaintiffs do—it is subject to liability for “discrimination.”

Second, the Rule mandates revisions to healthcare professionals’ written policies, requiring express affirmance that transition-related procedures will be provided. 81 Fed. Reg. at 31455. If a covered entity does not revise its written policies—even when doing so would contradict its religious beliefs and medical judgment—it again faces liability. Third, the Rule requires physicians to use gender-transition affirming language, including “a transgender individual’s preferred name and pronoun.” *See, e.g.*, 81 Fed. Reg. at 31406. Failure to do so again results in liability. *See, e.g.*, Compl., *Prescott v. Rady Children’s Hosp. - San Diego*, No. 16-2408 (S.D. Cal. Sept. 26, 2016) (suing a hospital under the new Rule for failing to use a patient’s preferred pronoun). In short, to avoid liability under the new Rule, healthcare professionals must avoid expressing the viewpoint that medical transition procedures are “experimental”; they must revise their written policies to endorse transition-related services; and they must use language that affirms gender transition.

Under the Free Speech Clause, however, the government cannot prohibit health providers from speaking about their own medical judgment simply because the government dislikes the content

of that speech. For example, in *Sorrell v. IMS Health Inc.*, 564 U.S. 552, 566 (2011), the Supreme Court struck down a state regulation prohibiting pharmacies from selling information about prescribing practices to drug manufacturers for marketing purposes. *Id.* at 567. The Court noted that the state had “imposed a restriction on access to information in private hands,” and the “law impose[d] a burden based on the content of speech and the identity of the speaker.” *Id.* at 567-68. Even under the more relaxed scrutiny applied to “commercial speech,” the Court held the state’s interests in medical privacy, improved public health, and reduced healthcare costs did not “withstand[] scrutiny.” *Id.* at 571-72.

Even more relevant here, in *Conant v. Walters*, 309 F.3d 629, 637 (9th Cir. 2002), the Ninth Circuit struck down a government policy that sought “to punish physicians on the basis of the content of doctor-patient communications.” Specifically, the government sought to punish a “physician’s professional ‘recommendation’ of the use of medical marijuana.” *Id.* at 632. The court held that this policy “strike[s] at core First Amendment interests of doctors and patients,” because an “integral component of the practice of medicine is the communication between a doctor and a patient. Physicians must be able to speak frankly and openly to patients.” *Id.* at 636.

The government’s regulation of speech is even more troubling than in *Sorrell* or *Conant*. First, unlike the speech in *Sorrell*, which included records sold for a profit to marketers, Plaintiffs are speaking based on their best medical and religious judgment, and they are forgoing profit rather than seeking it. *Cf. Conant*, 309 F.3d at 639-640 (Kozinski, J., concurring). Second, more than just prohibiting Plaintiffs’ dissemination of certain information to certain parties, HHS’s Rule deems a particular medical viewpoint to be discriminatory—namely, the viewpoint that transition-related treatment is “experimental.” 81 Fed. Reg. at 31435; *see also id.* at 31429. HHS rejects this viewpoint as “outdated and not based on current standards of care,” and approvingly cites another HHS

document stating that “sex reassignment surgery *can no longer be considered* an experimental treatment.” *Id.* at 31435 & n.263 (citing Ex. J at 23 (HHS Appeals Board Decision)). It also compels providers to revise their written policies to endorse medical transition procedures and to use language that is affirming of gender transition. Thus, HHS treats the expression of certain medical and religious viewpoints about gender transition procedures as illegal discrimination.

Plaintiffs hold those viewpoints. *See* Ex. A, ¶ 9 (Sister O’Brien Decl.); Ex. D, ¶ 11 (Sister Hart Decl.); Ex. E, ¶ 5 (Dr. Twanow Decl.). Plaintiffs are unwilling to revise their written policies to affirm and offer gender transition procedures, as required by the Rule. Ex. A, ¶ 11 (Sister O’Brien Decl.); Ex. B, ¶ 8 (Sister Stahl Decl.). *See, Agency for Int’l Dev. v. All. for Open Soc’y Int’l, Inc.*, 133 S. Ct. 2321, 2330-31 (2013) (rejecting requirement that federal grant recipients adopt policy opposing prostitution). And Plaintiffs, such as the Religious Sisters of Mercy, are unwilling to use gender-transition affirming language, such as “a transgender individual’s preferred name and pronoun,” because doing so would violate their religious beliefs and medical judgment. Ex. D, ¶ 12 (Sister Hart Decl.). For their viewpoints, Plaintiffs are subject to enforcement proceedings, loss of federal funding, and private lawsuits under the Rule. “When the government targets not subject matter, but particular views taken by speakers on a subject, the violation of the First Amendment is all the more blatant.” *Rosenberger v. Rector*, 515 U.S. 819, 829 (1995). Such content-based restrictions on speech are “presumptively invalid.” *R.A.V. v. St. Paul*, 505 U.S. 377, 382 (1992).²⁴

V. The Rule is unconstitutionally vague

The Rule also violates the Due Process Clause and First Amendment because it is hopelessly vague. “A fundamental principle in our legal system is that laws which regulate persons or entities

²⁴ For the same reasons the Rule fails strict scrutiny under RFRA, it also fails strict scrutiny under the Speech Clause. *See O Centro*, 546 U.S. at 429-30 (regardless of whether strict scrutiny is triggered by the Free Speech Clause or RFRA, “the consequences are the same”).

must give fair notice of conduct that is forbidden or required.” *F.C.C. v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012). A law is impermissibly vague where it allows the government to rely on “untethered” and “wholly subjective judgments without statutory definitions, narrowing context, or settled legal meanings.” *Holder v. Humanitarian Law Project*, 561 U.S. 1, 20-21 (2010). A law cannot be “so standardless that it authorizes or encourages seriously discriminatory enforcement.” *United States v. Williams*, 553 U.S. 285, 304 (2008). And when protected expression is being potentially swept into the reach of a law, “rigorous adherence to those requirements is necessary to ensure that ambiguity does not chill protected speech.” *Fox*, 132 S. Ct. at 2317.

The Rule fails these constitutional requirements. Under the sweeping new definition of “sex,” health care providers are left to guess at the type of action (or inaction) that might result in crippling liability. Further, in the face of HHS’s vague prohibitions on certain types of expression, healthcare professionals face serious pressure to self-censor in order to avoid liability.

A. The Rule fails to give fair notice of what conduct is subject to liability and gives HHS ample room for arbitrary enforcement.

“Even when speech is not at issue, the void for vagueness doctrine” requires that “regulated parties should know what is required of them so they may act accordingly.” *Fox*, 132 S. Ct. at 2317 (citing *Grayned v. City of Rockford*, 408 U.S. 104, 108-109 (1972)). “[P]recision and guidance are necessary so that those enforcing the law do not act in an arbitrary or discriminatory way.” *Id.*

Here, HHS specifically rejected commenters’ repeated requests for “further information on the application of the rule to specific circumstances.” 81 Fed. Reg. at 31377. Instead, HHS stated, “we neither address every scenario that might arise in the application of these standards nor state that certain practices as a matter of law are ‘always’ or ‘never’ permissible. The determination of whether a certain practice is discriminatory typically requires a nuanced analysis that is fact-dependent.” *Id.* HHS in fact boasted that it “value[s] the flexibility inherent in the contextualized

approach we have chosen to assess compliance.” *Id.* at 31419. But HHS has left itself so much flexibility that there is nothing to prevent it from “act[ing] in an arbitrary or discriminatory way” when it enforces the Rule. *Fox*, 132 S. Ct. at 2317.

For example, regarding prohibitions on discriminatory insurance coverage, the Rule “require[s] that a covered entity apply the same neutral, nondiscriminatory criteria that it uses for other conditions when the coverage determination is related to gender transition.” 81 Fed. Reg. at 31435. Yet HHS provides no clear guidance on what qualifies as “neutral, nondiscriminatory criteria.” For instance, HHS pays lip service to the idea that it “will not second-guess a covered entity’s neutral nondiscriminatory application of evidence-based criteria used to make medical necessity or coverage determinations.” *Id.* at 31436-37. But HHS also “decline[s] to limit application of the rule by specifying that coverage for the health services . . . must be provided *only* when the services are *medically necessary or medically appropriate*.” 81 Fed. Reg. at 31435 (emphasis added). In other words, HHS reserves the right to impose liability even when a covered entity determines that a procedure is *not* “medically necessary or medically appropriate.” *Id.*

By removing the most obvious types of “neutral” criteria on which covered entities have historically relied—limiting coverage to procedures that are medically necessary, medically appropriate, and that are not merely cosmetic or experimental—HHS has left covered entities with no clear criteria to choose from. And because covered entities lack “fair notice of what is prohibited” under the Rule, Plaintiffs are pressured to provide coverage for any transition-related procedure an employee’s provider recommends. *See Williams*, 553 U.S. at 304.

The Rule also bans discriminatory “benefit design” for an insurance plan—without explaining what a “benefit design” even is. Not surprisingly, HHS received many “requests for guidance and clarification regarding potentially discriminatory benefit designs and suggestions for scenarios that

constitute per se discrimination.” 81 Fed. Reg. at 31433. But HHS refused:

[W]e decline to define ‘benefit design’ in the final rule because to do so would be overly prescriptive. We also decline to codify examples of discriminatory benefit designs because determining whether a particular benefit design results in discrimination will be a fact-specific inquiry that OCR will conduct through its enforcement of Section 1557. For the same reason, we avoid characterizing specific benefit design practices as per se discriminatory in the final rule.

Id. at 31433-34. This is a pathetic lack of guidance. Plaintiffs and other covered entities are designing complex insurance plans that affect thousands of employees. But under this Rule, they can do nothing but guess at what HHS will decide constitutes a discriminatory benefit design. And they must make those guesses on pain of massive financial liability.

Professionals providing healthcare services face the same dearth of guidance. HHS states that “providers of health services may no longer deny or limit services based on an individual’s sex, without a legitimate nondiscriminatory reason.” 81 Fed. Reg. at 31455. But HHS offers no guidance on what will qualify as “a legitimate nondiscriminatory reason.” For many years, doctors have deemed medical transition procedures experimental or harmful based on the current status of the medical literature. But now HHS says that a “categorization of all transition-related treatment . . . as experimental, is outdated and not based on current standards of care.” 81 Fed. Reg. at 31435.

At the same time, HHS offers no guidance on what the applicable standards of care actually are. Indeed, HHS “decline[d] to include a definition of ‘health services related to gender transition’” but instead “intends to interpret these services broadly and recognizes that health services related to gender transition may change as standards of medical care continue to evolve.” *Id.* Nor did HHS provide guidance on whether physicians can rely on their best medical judgment when it conflicts with this Rule. This stands in sharp contrast with the regulations governing the military’s TRICARE plan, which provides a clear safe harbor, stating: “In no circumstance will a provider be required to deliver care that he or she feels unprepared to provide either by lack of clinical skill

or due to ethical, moral, or religious beliefs.” *See* Ex. I at 2-3 (TRICARE Memo).

In short, the new Rule places healthcare professionals, including Plaintiffs, in the unprecedented position of being forced to perform or cover procedures that violate their medical judgment or else face crippling liability—with the agency deliberately choosing to withhold clear guidance about how to walk the tightrope between the two. The result is an unconstitutionally vague rule that “trap[s] the innocent by not providing fair warning.” *Grayned*, 408 U.S. at 108.

B. The Rule’s vague, overbroad, and content-based restrictions result in a serious chilling effect on protected expressive activity.

The vagueness here is all the more troubling because it chills constitutionally protected activity: “The vice of unconstitutional vagueness is further aggravated where, as here, the [rule] in question operates to inhibit the exercise of individual freedoms affirmatively protected by the Constitution.” *Cramp v. Bd. of Pub. Instruction of Orange Cty., Fla.*, 368 U.S. 278, 287 (1961). A law that “threatens to inhibit the exercise of constitutionally protected rights,” such as “the right of free speech,” is subject to “a more stringent vagueness test.” *Vill. of Hoffman Estates v. Flipside, Hoffman Estates, Inc.*, 455 U.S. 489, 499 (1982). Indeed, “[w]hen speech is involved, rigorous adherence to” the requirements to give fair notice and provide precise guidance regarding enforcement “is necessary to ensure that ambiguity does not chill protected speech.” *Fox*, 132 S. Ct. at 2317.

HHS may argue that it does not plan to enforce the Rule to punish protected speech. But there is no question that the Rule’s “literal scope, unaided by a narrowing . . . court interpretation, is capable of reaching expression sheltered by the First Amendment.” *Smith v. Goguen*, 415 U.S. 566, 573 (1974). The Rule says that medical views opposed to medical transition procedures are “outdated” and discriminatory, and it compels transition-affirming speech such as revised policies and preferred pronouns. 81 Fed. Reg. at 31435, 31429. In such circumstances, those who wish to avoid liability can do so “only by restricting their conduct to that which is unquestionably safe.”

Baggett v. Bullitt, 377 U.S. 360, 372 (1964); *see, e.g.*, Ex. A, ¶ 11 (Sister O’Brien Decl.). Thus, the Rule falls short of the “greater degree of specificity” required when it “abut[s] upon sensitive areas of basic First Amendment freedoms.” *Goguen*, 415 U.S. at 573; *Baggett*, 377 U.S. at 372.

VI. A preliminary injunction is required.

The Court should enter a preliminary injunction against the Rule before January 1, 2017—which is when Plaintiffs will be forced to make significant, expensive changes to their insurance plans. When issuing a preliminary injunction, the Court considers (1) the movant’s likelihood of success on the merits, (2) the threat of irreparable harm to the movant, (3) the balance of harms between the parties, and (4) the public interest. *Sharpe Holdings*, 801 F.3d at 936–37.

Likelihood of Success on the Merits. As shown above, Plaintiffs are highly likely to succeed on the merits of all their claims. This is the most significant preliminary injunction factor, *id.*, and in cases like this one, where First Amendment rights are at stake, “the analysis begins and ends with the likelihood of success on the merits,” *Korte v. Sebelius*, 735 F.3d 654, 666 (7th Cir. 2013); *see also Hobby Lobby*, 723 F.3d 1114, 1146 (10th Cir. 2013) (“[O]ur case law analogizes RFRA to a constitutional right.”), *aff’d sub nom. Burwell v. Hobby Lobby*, 134 S. Ct. 2751 (2014).

Irreparable Harm. It is settled law that a potential violation of Plaintiffs’ rights under the First Amendment and RFRA threatens irreparable harm. “The loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury.” *Iowa Right to Life Comm., Inc. v. Williams*, 187 F.3d 963, 970 (8th Cir. 1999) (quoting *Elrod v. Burns*, 427 U.S. 347, 373 (1976)). Here, coercing Plaintiffs to provide harmful medical procedures or objectionable insurance coverage in direct violation of their faith is the epitome of irreparable injury. Once they have been forced to violate their conscience, future remedies cannot undo the past.

The same principle applies to the harm to Plaintiffs from the government’s violations of the Administrative Procedure Act, Due Process Clause, and Spending Clause. Absent an injunction,

they must either violate their faith and suffer the substantial costs of complying with an invalid Rule, *see* 81 Fed. Reg. 31455-57 (estimating costs), or violate the Rule and face large financial penalties, 45 C.F.R. § 92.301. Those harms cannot be compensated by damages; they can only be prevented. *Cf. Texas v. E.P.A.*, 829 F.3d 405, 434 (5th Cir. 2016) (finding irreparable harm because “[n]o mechanism here exists for [plaintiffs] to recover the compliance costs they will incur if the Final Rule is invalidated on the merits.”).

The Rule also threatens irreparable harm to North Dakota by upending its current laws and policies governing its health care facilities and by invalidating religious accommodations for state employees. *See supra* Statement of Facts, Part F. A State suffers irreparable harm when its laws or policies are enjoined. *New Motor Vehicle Bd. of Cal. v. Orrin W. Fox Co.*, 434 U.S. 1345, 1351 (1977). Here, the Rule strips North Dakota of its right to enforce its own laws in its healthcare programs and workplaces, requires State healthcare facilities to offer transition and abortion procedures, and requires the State to train employees about obligations under the Rule. North Dakota did not agree to these requirements when it chose to participate in Medicare and Medicaid decades ago. This amounts to irreparable harm to its sovereign interest. *See Kansas v. United States*, 249 F.3d 1213, 1227 (10th Cir. 2001) (erroneous tribal gaming commission decision amounts to irreparable injury to state’s sovereign interest).

Balance of Harms. Since Plaintiffs are likely to succeed, Defendants must “present powerful evidence of harms to [their] interests” to prevent Plaintiffs from meeting the balancing requirement. *Opulent Life Church v. City of Holly Spring, Miss.*, 697 F.3d 279, 297 (5th Cir. 2012). Here, the harms faced by Plaintiffs are severe, and the harms to Defendants are minimal. HHS has acknowledged that its goals need not be achieved immediately or uniformly, a fact made plain by its decision to wait *six years* after enactment of the ACA to promulgate the Rule—and to exempt

its own insurance programs from its effect. HHS claimed that the Rule “would not displace the protections afforded by provider conscience laws, the Religious Freedom Restoration Act (RFRA), provisions in the ACA related to abortion services, or regulations issued under the ACA related to preventive health services.” 81 Fed. Reg. at 31378-79. Those are the very protections invoked here. “[W]here the regulation [is underinclusive and] fails to address significant influences that impact the purported interest, it usually flushes out the fact that the interest does not rise to the level of being ‘compelling’ ... enough to justify abridging core constitutional rights...” 281 *Care Comm.*, 766 F.3d at 785 (second alteration in original). The same is true for unlawful government action which places heavy burdens on the sovereign interests of states. *See Texas v. United States*, 809 F.3d 134, 187 (5th Cir. 2015), *as revised* (Nov. 25, 2015), *aff’d by divided court* 136 S. Ct. 2271 (2016), *reh’g denied*, 2016 WL 5640497 (Mem.) (Oct. 3, 2016).

Public Interest. “This factor overlaps considerably with the previous one, and most of the same analysis applies.” *Texas*, 809 F.3d at 187. “[I]njuncts protecting First Amendment freedoms are always in the public interest.” *Christian Legal Soc’y v. Walker*, 453 F.3d 853, 859 (7th Cir. 2006). Moreover, stripping Plaintiffs of Medicare and Medicaid funding hurts the vulnerable people that depend on Plaintiffs’ health services—both the poor and elderly, and those in rural areas that depend on Plaintiffs’ critical access to hospitals. Given the gravity of the changes proposed in the Rule, the medical debate on the propriety of these procedures, the widespread impact on private and public entities, the harm to citizens who rely upon Plaintiffs for medical treatment, and the intrusion into sovereignty, the public interest favors an injunction.

CONCLUSION

The motion should be granted.

Respectfully submitted this the 17th day of November, 2016.

<u>/s/ Luke W. Goodrich</u> Luke W. Goodrich Stephanie H. Barclay The Becket Fund for Religious Liberty 1200 New Hampshire Ave. NW Suite 700 Washington, DC 20036 Telephone: (202) 349-7216 Facsimile: (202) 955-0090 lgoodrich@becketfund.org <i>Counsel for Plaintiffs Religious Sisters of Mercy, Sacred Heart Mercy Health Care Center (Jackson, MN); Sacred Heart Mercy Health Care Center (Alma, MI); SMP Health System, and University of Mary</i>	<u>/s/ Wayne Stenehjem</u> Wayne Stenehjem Attorney General of North Dakota 600 E. Boulevard Avenue Bismarck, ND 58505-0040 Telephone: (701) 328-2210 Facsimile: (701) 328-2226 Douglas A. Bahr Solicitor General N.D. Office of Attorney General 500 N. 9th Street Bismarck, ND 58501 Telephone: (701) 328-3640 Facsimile: (701) 328-4300 <i>Counsel for Plaintiff North Dakota</i>

CERTIFICATE OF SERVICE

I hereby certify that on November 17, 2016 the foregoing memorandum was served on Defendants via email in accordance with Defendants' consent to receive service via email.

/s/ Luke W. Goodrich
Luke W. Goodrich

EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTH DAKOTA
EASTERN DIVISION

THE RELIGIOUS SISTERS OF
MERCY, *et al.*,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants

No. 3:16-cv-00386-RRE-ARS

**Declaration of Sister Mary Judith
O'Brien, R.S.M., J.C.D.**

1. My name is Sister Mary Judith O'Brien. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. § 1746. I have not been convicted of a felony or crime involving dishonesty. The facts contained herein are within my personal knowledge. If I were called upon to testify to these facts, I could and would competently do so.

2. I am a Religious Sister within the Religious Sisters of Mercy, a Catholic order of religious sisters devoted to works of mercy, including offering healthcare to the underserved. I received my licentiate and doctorate, *magna cum laude*, at the Pontifical Gregorian University in Rome in 1994. I am also a civil lawyer. For the past eleven years, I have worked for the Diocese of Saginaw, first as

Vice-Chancellor and now as Chancellor—a position I have held for seven years. Before my assignment in Saginaw, I worked in the Archdiocese of Denver, helping to establish St. John Vianney Seminary and serving as chair of the Department of Pastoral Theology. In Denver, I collaborated with the Archbishop's office in a variety of canonical and civil law projects. I currently serve on the board for both Sacred Heart Mercy Health Care Center clinics, which are owned and operated by the Religious Sisters of Mercy.

3. Located in Alma, Michigan, the Religious Sisters of Mercy is a nonprofit corporation incorporated in 1973. The Religious Sisters of Mercy are an international institute of pontifical right—that is, officially approved by the Vatican—which traces its roots back to Venerable Catherine McAuley in Dublin, Ireland in 1831.

4. As Religious Sisters of Mercy, we have chosen to follow Jesus Christ by taking a lifetime vow to serve the poor and sick by offering care for the whole person, and working to heal those who are suffering from physical, psychological, intellectual, and spiritual woundedness. The Religious Sisters of Mercy offer a variety of apostolic services. One aspect of our mission is fulfilled through “comprehensive health care” services, which we understand as “the complete care of the total human person” which “seeks to bring about that profound and extensive healing which is a continuation of the work of redemption.”

5. Consistent with this mission, some of the Religious Sisters of Mercy serve in healthcare facilities, such as hospitals, throughout the country. These Sisters include licensed doctors, including a surgeon, and other healthcare professionals. In accordance with their vows, the Religious Sisters of Mercy offer healthcare services in accordance with the Ethical and Religious Directives of the United States Conference of Catholic Bishops and our Catholic faith. For decades, the religious beliefs of the Religious Sisters of Mercy have been respected by health institutions where they work.

I. The Sacred Heart Clinics

6. The Religious Sisters of Mercy own and operate two clinics, Sacred Heart Mercy Health Care Center in Alma, Michigan, and Sacred Heart Mercy Health Care Center in Jackson, Minnesota. Both are nonprofits incorporated in their respective states. The Religious Sisters of Mercy also run their clinics in accordance with the Ethical and Religious Directives of the United States Conference of Catholic Bishops. These clinics contain religious chapels and prominently display religious iconography. Some of the Religious Sisters of Mercy serve as licensed doctors, nurses, or other healthcare professionals who perform medical services in these clinics.

7. The Religious Sisters of Mercy at the Sacred Heart clinics strive to provide top-quality care to their patients. They serve and respect individuals of all faiths, and seek to ensure that patients and their families can exercise their own

faith traditions in order to assist them in the healing and recovery process, and to make critical decisions about matters such as end-of-life care and clinical ethics.

8. The clinics further the Sisters' mission to care for the elderly and the poor by serving Medicare and Medicaid patients and also provide low-cost or free care to the uninsured. A significant portion of the patients served by the Sacred Heart clinics are poor, disabled, and elderly Medicare and Medicaid patients. If the Sacred Heart clinics lost this HHS funding, the clinics would suffer a crippling blow to their capacity to carry out their religious mission to serve the poor, disabled, and elderly.

9. The Religious Sisters of Mercy hold religious beliefs about the nature and purposes of human sexuality. Like the Catholic Church they serve, the Religious Sisters of Mercy believe that every man and woman is created in the image and likeness of God, and that they reflect God's image in unique—and uniquely dignified—ways.

10. Further, in their professional medical judgment, the Religious Sisters of Mercy who work in health care believe that optimal patient care—including patient education, diagnosis, and treatment—requires taking account of the biological differences between men and women.

11. In the Sisters' best medical judgment, providing or assisting with gender transition services is not in keeping with the best interests of their patients, and in fact is experimental and could be harmful for patients.

12. Providing services that are contrary to their understanding of God's plan for human sexuality would also violate the religious exercise of the Religious Sisters of Mercy.

II. Insurance Coverage

13. As part of their religious beliefs, the Sacred Heart clinics also offer health benefits to eligible employees who work for the clinics. It would violate the religious beliefs of the Sacred Heart clinics and the Sisters who own and operate them if they were forced to offer a health plan that included benefits for abortions, sterilizations, or any drugs or procedures related to gender transition. The Sacred Heart clinics and the Sisters who own and operate them sincerely believe that such coverage would constitute impermissible material cooperation with evil.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 16, 2016.

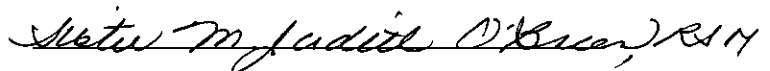

Sister Mary Judith O'Brien, R.S.M., J.C.D.

EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTH DAKOTA
EASTERN DIVISION

THE RELIGIOUS SISTERS OF
MERCY, *et al.*,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants

No. 3:16-cv-00386-RRE-ARS

**Declaration of Sister Suzanne
Stahl**

1. My name is Sister Suzanne Stahl. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. § 1746. I have not been convicted of a felony or crime involving dishonesty. The facts contained herein are within my personal knowledge. If I were called upon to testify to these facts, I could and would competently do so.

2. I am a Sister of Mary of the Presentation from Valley City, North Dakota. I presently serve as Provincial of the Sisters of Mary of the Presentation, and I have done so since 2014. Prior to that, I was the Provincial Assistant for nine years. I work at Maryvale, the Provincial Home of the Sisters of Mary of the

Presentation. I previously lived and worked at some of our Religious Congregation's missions in the United States and Africa.

3. The Sisters of Mary of the Presentation were founded in France in 1828 for the purpose of teaching children and serving the sick, disabled, and elderly. In 1903, fleeing religious persecution in France, the Sisters arrived in the United States and began a school in Wild Rice, North Dakota and a hospital in Spring Valley, Illinois. The Sisters of Mary of the Presentation now have a Provincial home in Valley City, North Dakota, and operate three critical access hospitals in North Dakota, in addition to the original hospital in Spring Valley. The Sisters also operate five nursing homes to serve the elderly in North Dakota. Together, these ministries constitute SMP Health System.

4. SMP Health System is operated according to the religious beliefs of its sponsor, the Sisters of Mary of the Presentation. The mission of SMP Health System is to "provide[] leadership to its Catholic health care ministries as they work to fulfill the healing mission of Jesus." SMP Health System's vision statement explains that "Our concern is for all people, but the poor and elderly have a special claim on us. From our limited resources we provide services characterized by excellence, compassion, and personalized concern. Because we care, we focus on the needs of the whole person, physical, spiritual, psychological, and social." See SMP Health System, *Mission, Values, Vision and Philosophy*, <http://smphs.org/mission-values-vision-philosophy.html> (last visited Nov. 7, 2016). Thus, SMP Health System

has a special emphasis on providing services to the poor and elderly, including many Medicare and Medicaid patients. If SMP Health System lost HHS funding, it would suffer a serious blow to its capacity to carry out that mission.

5. In accordance with this vision and mission, the Sisters of Mary of the Presentation operate SMP Health System in a manner that abides by *The Ethical and Religious Directives for Catholic Healthcare Services*, as issued by the United States Conference of Catholic Bishops and interpreted by the local Bishop. The Sisters of Mary of the Presentation strive to “provide quality patient care in an environment that contributes to the healing of the whole person.”

6. Like the Catholic Church it serves, SMP Health System believes that every man and woman is created in the image and likeness of God and reflects God’s image in unique—and uniquely dignified—ways. Being forced to provide or facilitate gender transition services would violate the religious beliefs of SMP Health System.

7. SMP Health System provides all of its standard medical services with dignity and compassion to every individual who needs and qualifies for its care, including to individuals who identify as transgender. Thus, for instance, if a transgender individual comes in with high blood pressure or a diabetes diagnosis, SMP Health System would provide the same full spectrum of compassionate care for that individual as they provide for every other patient. And, just as we do for

every other patient, SMP Health System would appropriately tailor that care to the biologically sex-specific health needs of the patient.

8. The SMP Health System physicians and facilities offer services such as hysterectomies, mastectomies, endocrinology services, and psychiatric support. In certain contexts, SMP Health System physicians also offer endocrinology services to pediatric patients, including children. It would violate SMP Health System's religious beliefs if we were forced to require physicians to offer these services for a gender transition.

9. Some of the procedures required under the Rule, including elective hysterectomies, can result in the sterilization of the patient. It would violate SMP Health System's religious beliefs if it were required to offer elective medical services that resulted in a sterilization.

10. In certain contexts, SMP Health System performs surgical procedures for women who have miscarried a baby, such as dilation and curettage. It would violate SMP Health System's religious beliefs if it were required to offer this procedure to terminate a pregnancy.

11. As part of its religious beliefs, SMP Health System offers health benefits to its full time employees. It would violate the religious beliefs of SMP Health System if it were forced to offer a health plan that included benefits for abortions, sterilizations, or any drugs or procedures related to gender transition. SMP Health System and the Sisters of Mary of the Presentation sincerely believe

that offering such coverage would constitute impermissible material cooperation with evil.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 15, 2016.

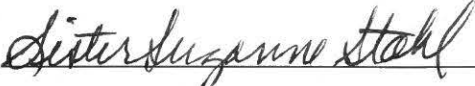

Sister Suzanne Stahl

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTH DAKOTA
EASTERN DIVISION

THE RELIGIOUS SISTERS OF
MERCY, *et al.*,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants

No. 3:16-cv-00386-RRE-ARS

**Declaration of Monsignor James
Patrick Shea**

1. My name is Monsignor James Patrick Shea. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. § 1746. I have not been convicted of a felony or crime involving dishonesty. The facts contained herein are within my personal knowledge. If I were called upon to testify to these facts, I could and would competently do so.

2. In 2009, I was inaugurated as the sixth President of the University of Mary—a position I still hold. I began my undergraduate work at Jamestown College, studying English and history. I then entered the seminary for the Diocese of Bismarck, earning a bachelor's degree and a pontifical master's degree (licentiate) in philosophy at the Catholic University of America in Washington, D.C. I studied classical Greek at the University of Texas at Austin and continued at the Vatican's North American College, studying theology at the Gregorian and Lateran universities in Rome. I have studied management at the University of Chicago's Graduate School

of Business and I am also an alumnus of the Institutes for Higher Education at the Graduate School of Education, Harvard University.

3. I am a Knight Commander of the Holy Sepulchre of Jerusalem, and I serve on the Board of Directors for FOCUS, the Fellowship of Catholic University Students. I have served on the National Advisory Council to the United States Conference of Catholic Bishops and the Governor's Commission on Education Improvement for the State of North Dakota. I am also a Trustee of Saint John Vianney Seminary in Denver and a member of the Executive Committee of the Board for the Association of Benedictine Colleges and Universities.

4. The University of Mary has a long tradition of carrying out the mission of Jesus Christ through education. In 1878, a brave group of Benedictine Sisters arrived in Dakota Territory to bring ministries of healing and learning, founding schools and hospitals to serve the community.

5. In 1959, the Benedictine Sisters of the Annunciation founded Mary College, offering degrees in education and nursing. Over time, the college expanded and added additional programs. In the 1980s, it added its first graduate program, in nursing, and became the University of Mary.

6. The University strives to infuse all of its programs with Christian, Catholic, Benedictine values to prepare its students to be ethical leaders in their careers and their communities. The University welcomes students of all faiths and

backgrounds and, as is fundamental to its mission, upholds Catholic teaching in all of its programs and services.

7. For example, the University's freshman and sophomore students are required to live on campus. The University residence life program has been designed to be a co-curricular student learning program. The program is structured to help students learn by participating in a residence life community where the programming and policies are designed to encourage students to practice Christian virtues and the University's Benedictine values.

8. The University has a long history of offering medical education inspired by its Catholic faith. For example, the University is one of only a few in the United States to offer a master's degree in bioethics, designed to help professionals make morally sound decisions about responsible use of biomedical advances. The program is offered in partnership with the National Catholic Bioethics Center.

9. As it has since its founding, the University offers a nursing program. It provides several nursing degrees at the undergraduate, graduate and doctoral level. The University's nursing program on June 17, 2016 received a three-year grant for over \$1 million from the Department of Health and Human Services. That grant is intended to aid in training nurses to improve rural healthcare in North Dakota.

10. The University holds religious beliefs that sexual identity is an objective fact rooted in nature as male or female persons. The University believes that every

man and woman is created in the image and likeness of God and that they reflect God's image in unique—and uniquely dignified—ways.

11. The University also has a student health clinic that operates in accordance with the Ethical and Religious Directives of the United States Conference of Catholic Bishops. It would violate the University of Mary's religious beliefs if it were forced to use this health clinic to provide or facilitate services for a gender transition or abortion.

12. As part of its religious beliefs, the University offers health benefits to its employees. The University has over 360 employees. Approximately 347 of these employees are eligible for health insurance benefits from the University.

13. The University operates a self-funded health plan which provides coverage for its employees through a third-party administrator. The same plan provides coverage for all employees, whether in the nursing program or outside the nursing program.

14. It would violate the religious beliefs of the University if it were forced to offer a health plan that included benefits for abortions, sterilizations, or any drugs or procedures related to gender transition. The University sincerely believes that offering such coverage would constitute impermissible material cooperation with evil.

15. The Regulation also makes it more expensive for the University to work with its third-party administrator. The Regulation subjects the third-party administrator to potential liability for administering the University's religious health

plan, and we expect that the third-party administrator will require us to indemnify it for this potential liability.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 17, 2016.

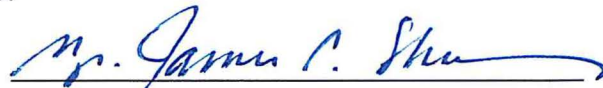

Monsignor James Patrick Shea

EXHIBIT D

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTH DAKOTA
EASTERN DIVISION

THE RELIGIOUS SISTERS OF
MERCY, *et al.*,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants

No. 3:16-cv-00386-RRE-ARS

Declaration of Sister Edith Mary
Hart, R.S.M., D.O.

1. My name is Sister Edith Mary Hart. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. § 1746. I have not been convicted of a felony or crime involving dishonesty. The facts contained herein are within my personal knowledge and medical judgment. If I were called upon to testify to these facts, I could and would competently do so.

2. I am both a licensed physician and a Religious Sister within the Religious Sisters of Mercy ("Sisters of Mercy"), a Catholic order of religious sisters devoted to works of mercy, including offering healthcare to the underserved. I graduated from Oklahoma State University College of Osteopathic Medicine in 2006. I completed my residency in Family Medicine at Sparrow Health

System/Michigan State University in 2010 and my fellowship in Geriatric Medicine from Michigan State University in 2011, and I am board certified in both specialties. I am currently serving at Sacred Heart Mercy Health Care Center in Jackson, Minnesota, where I practice outpatient Family Medicine.

3. I also work in the Emergency Department at Sanford Jackson Medical Center in Jackson, Minnesota, and serve as the Director of the ED and Trauma Services. In addition, I am the medical director of Sanford Hospice and at Good Samaritan Nursing Home in Jackson where I also care for residents. I also serve on the Board of Directors of Divine Mercy Supportive Care in the Archdiocese of Denver. As long as I have offered medical services as a physician, my medical judgment and religious beliefs has been respected by health institutions where I work.

4. As a Sister of Mercy, I have chosen to follow Jesus Christ by taking a lifetime vow to serve the poor and sick by offering care for the whole person, and working to heal those who are suffering from physical, psychological, intellectual, and spiritual woundedness. One aspect of our mission is fulfilled through "comprehensive health care" services, which we understand as "the complete care of the total human person" which "seeks to bring about that profound and extensive healing which is a continuation of the work of redemption." I work to fulfill this mission, in part, by seeking to understand the root causes of issues affecting my

patients, and to address underlying causes directly rather than masking issues through offering ineffective treatments.

5. In every healthcare setting where I serve, I strive to provide top-quality and compassionate care to all of my patients. I also ensure that I provide medical services and advice in accordance with the Ethical and Religious Directives of the United States Conference of Catholic Bishops and my own Catholic faith.

6. Through my work as a physician at the Sacred Heart clinic, I have the opportunity to serve and respect individuals of all faiths and walks of life, including multiple patients of mine who identify as gay or lesbian. I offer medical services to both adults and children, including infants. A significant portion of the patients I serve at the Sacred Heart clinic are also poor, disabled, and elderly Medicare and Medicaid patients. The clinics further the Sisters' mission to care for the elderly and the poor by serving Medicare and Medicaid patients and also provide low-cost or free care to the uninsured. If the Sacred Heart clinic lost this HHS funding, we would suffer a crippling blow in our capacity to carry out our religious mission to serve the poor, disabled, and elderly.

7. I hold religious beliefs about the nature and purposes of human sexuality. I believe that every man and woman is created in the image and likeness of God, and that they reflect God's image in unique—and uniquely dignified—ways.

8. Further, in my professional medical judgment, I believe that optimal patient care—including patient education, diagnosis, and treatment—requires taking account of the biological differences between men and women.

9. In my best medical judgment, providing or assisting with gender transition services is not in keeping with the best interests of patients, and in fact is experimental and could be harmful for patients.

10. As part of my normal medical practice, I sometimes prescribe hormones to patients with medical issues, such as a woman going through menopause with insufficient estrogen. If I were asked to prescribe hormones to individuals for a gender transition purpose, such as prescribing estrogen to a male, I would not be able to do so in light of my medical judgment and religious beliefs.

11. As part of my normal medical practice, I sometimes counsel patients with mental health issues, including children or youth who suffer from anxiety or depression. I explore with these patients alternatives to alleviate their mental distress, and sometimes I prescribe medication to address issues such as anxiety. If I were asked to explore the possibility of a gender transition with a patient as a viable alternative to alleviate mental distress, or to affirm a non-binary view of gender, I would not be able to do so in light of my medical judgment and religious beliefs.

12. I would also not be able to refer to patients with transgender pronouns or names if they requested that I do so. I believe that using transgender pronouns

would simply aggravate an issue of identity and self-perception, and further mask a deeper underlying issue. In my medical judgment, this would not be doing a service to my patients. Being forced to use transgender pronouns and names would also violate my religious beliefs.

13. Providing services that are contrary to my understanding of God's plan for human sexuality would also violate my religious beliefs.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 16, 2016.



Sister Edith Mary Hart, R.S.M., D.O.

EXHIBIT E

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NORTH DAKOTA
EASTERN DIVISION

THE RELIGIOUS SISTERS OF
MERCY, *et al.*,

Plaintiffs,

v.

SYLVIA BURWELL, *et al.*,

Defendants

No. 3:16-cv-00386-RRE-ARS

**Declaration of Dr. Richard
Twanow, M.D.**

1. My name is Dr. Richard Twanow. I am over the age of 21 and am capable of making this declaration pursuant to 28 U.S.C. § 1746. I have not been convicted of a felony or crime involving dishonesty. The facts contained herein are within my personal knowledge and medical judgment. If I were called upon to testify to these facts, I could and would competently do so.

2. I obtained my medical degree from the University of Saskatchewan. I performed a family medicine residency at the Plains Health Center in Regina, Saskatchewan. I am certified by the Canadian College of Family Physicians, and I am also certified by the American Board of Family Practice. I am licensed to practice in the State of Illinois. I currently serve as the Chairman of the Board of

Directors for St. Margaret's Hospital in SMP Health System and have held that position since 2014. I have served on the Board of Directors for St. Margaret's Hospital since 2005. I have also served previously as Chairman of the Medicine/Family Medicine Committee, and I previously served as President of the medical staff for St. Margaret's Hospital. I am also a Clinical Assistant Professor at the University of Illinois, College of Medicine at Rockford. In addition, I am the Medical Director of a long term care facility called Aperion Care in Spring Valley, Illinois.

3. I have practiced family medicine for 40 years, 20 years of which have been at SMP Health System. My practice has included the full spectrum of family medicine, including in-patient care and emergency room work. My current practice of family medicine includes children, adults, and long term care.

4. SMP Health System provides all of its standard medical services with dignity and compassion to every individual who needs and qualifies for its care, including to individuals who identify as transgender. Thus, for instance, if a transgender individual comes in with high blood pressure or a diabetes diagnosis, SMP Health System would provide the same full spectrum of compassionate care for that individual as they provide for every other patient. And, just as we do for every other patient, SMP Health System would appropriately tailor that care to the biologically sex-specific health needs of the patient.

5. The SMP Health System physicians and facilities offer services such as hysterectomies, mastectomies, endocrinology services, and psychiatric support when medically indicated and in the patient's best interest. In certain contexts, SMP Health System physicians also offer endocrinology services to pediatric patients, including children, when medically appropriate. It would be a violation of SMP Health System's commitment to quality care for all patients if it were forced to offer these services for gender transition purposes, and thus it would violate SMP Health System's medical judgment if it were forced to offer these services for a gender transition purpose.

6. Such a requirement would interfere with the very important doctor-patient relationship, a relationship that is paramount to optimal patient care. SMP Health System also does not offer the full spectrum of care and expertise necessary to safely and effectively provide gender transition services to patients. SMP Health System would also object to forcing physicians to provide services that the physicians do not believe are in the best interest of their patients. In my medical judgment, it would not be safe or good medical care to force doctors to provide gender transition services when they do not have skills, knowledge, or facilities to do them correctly and safely for the patient.

7. SMP Health System physicians are encouraged to candidly discuss their medical opinions with their patients and offer medical advice freely about the risks of any procedure with patients. A requirement that inhibited a physician's

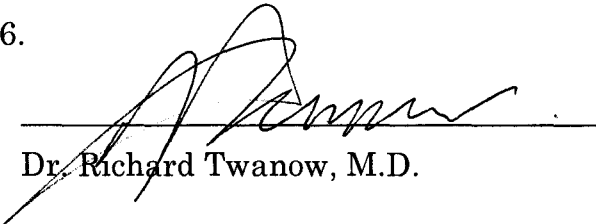
ability to engage in candid discussions with patients about the risks of gender transition procedures would be detrimental to optimal patient care.

8. Some of the procedures required under the Rule, including elective hysterectomies, can result in the sterilization of the patient, which SMP Health System also medically objects to providing.

9. In certain contexts, SMP Health System performs surgical procedures for women who have miscarried a baby, such as dilation and curettage, when medically indicated and in the patient's best interest. However, SMP Health System would be unwilling to offer the same service if the goal of the procedure was to terminate a pregnancy.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 17, 2016.



Dr. Richard Twanow, M.D.

EXHIBIT F

Proposed Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

[Back to Top](#)

Proposed Decision Memo

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Proposed Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: June 2, 2016

I. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance
APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Craps Experimental Index
CHIS - California Health Interview Survey
CI - Confidence Interval
CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Excerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Körpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King's Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale
SF - Short Form
SMR - Standardized Mortality Ratio
SOC - Standards of Care
STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
STAI-X2 - Spielberger State and Trait Anxiety Questionnaire

TSCS - Tennessee Self-Concept Scale

U.S. - United States

VAS - Visual Analog Scale

WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100

WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Therapeutic options for gender dysphoria include behavioral and psychotherapies, hormonal treatments, and a number of surgeries used for gender reassignment. This proposed decision is only focusing on gender reassignment surgery.

B. Prevalence of Gender Dysphoria

Prevalence of gender dysphoria estimates have been reported by several investigators.

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. The following states have at least 100 transgender beneficiaries: California, Florida, Georgia, Illinois, Massachusetts, Michigan, Minnesota, New York, Pennsylvania, Ohio, Texas, Washington, and Wisconsin. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. Of note, for the transgender population under age 65, the most prevalent chronic conditions were depression, major depressive affective disorder, and anxiety. Approximately 75% of transgender Medicare beneficiaries have been affected by depression, which is a disproportionately high amount compared to the Medicare population as a whole with 14% of Medicare fee-for-service beneficiaries suffering from the disease (CMS, *Chronic Conditions Among Medicare Beneficiaries*, 2012 at <https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/chronic-conditions/downloads/2012chartbook.pdf>). Based on the claims data, about 48% of transgender beneficiaries use hormone therapy, which are coverable under the Medicare Part D prescription drug benefit program (CMS Office of Minority Health (2015, June). New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. Paper presented at the Academy Health Annual Research Meeting, Minneapolis, Minnesota and Gay and Lesbian Medical Association Meeting, Portland, Oregon).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson, Moller 2003).

C. Interventions

Table 1 provides information about some of the types of therapeutic interventions for transgender individuals.

Table 1. Types of Therapeutic Intervention (May Not be Exhaustive)

Treatment Category	Male to Female	Female to Male
HORMONAL¹		
Core		
	Estrogens	Androgens Progestins/GnRH analogues for menses suppression as needed after 1 yr of androgens

Treatment Category	Male to Female	Female to Male
	Anti-androgens (e.g., spironolactone, 5- reductase blockers, androgen receptor blockers, GnRH analogues)	
SURGICAL^{2,3}		
Natal Internal Genital Removal	Orchidectomy (testes)	Hysterectomy (uterus) and Salpingo-oophorectomy (fallopian tubes + ovaries)
Natal External Genital Removal	Penectomy	NA
Breast Removal	NA	Mastectomy
Genital Reconstruction ²	Vaginoplasty Clitoroplasty Labiaplasty Urethrostomy	Metoidioplasty or Phalloplasty Inflatable/rigid penile prosthesis insertion Scrotal reconstruction

RH=gonadotropin releasing hormone NA=not applicable ?=possible =increased 2o=secondary

1—Bowman et al., 2012; Deutch, 2015; Elaut et al., 2010 Gooren et al., 2005 ,2013, and 2014; Heresova, 1986; Jacobeit, et al., 2009; Kronawitter et al., 2009; Meuller, 2010; Meyer et al., 1981; Pelusi et al., 2014; Schlatterer et al., 1998; Seal et al., 2012; Traish et al., 2010; Wierckx et al., 2011b, 2014; Williamson et al., 2010.

2—Revisions may be required. Kuhn et al., 2011.

3—Goddard et al., 2007a; Jain, Bradbeer, 2007; Selvaggi, Bellringer, 2011; Wroblewski et al., 2013.

III. History of Medicare Coverage

CMS does not currently have an NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a national coverage analysis (NCA) for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A)

Under §1832 (Scope of Part B)

Under §1861(s) (Definition of Medical and Other Health Services)

Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Table 2: Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
August 1, 1989	The Health Care Financing Agency (HCFA; predecessor agency to CMS) published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.
December 3, 2015	CMS accepts an external request to open an NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.

V. FDA Status

Surgical procedures *per se* are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved/cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited by the requestor, in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies evaluating therapeutic interventions for gender dysphoria. There was particular emphasis on the various surgical interventions, but other treatments including hormone therapy, psychotherapy, psychiatric treatment, ancillary reproductive and gender modifying services, and post-operative surveillance services for natal sex organs were also included because of their serial and sometimes overlapping roles in patient management. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) AND/OR quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), employment status, relationships, other social function, suicide (attempts), mortality, sexual function, urinary function, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). That is because when evaluating patients with this condition most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early termination, completed, and ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. The CMS internal search was limited to articles published prior to March 21, 2016. CMS reviewed results of clinical trials involving adult human subjects; to reports of prospective (e.g., blinded, non-blinded, cross sectional), partially prospective, retrospective longitudinal studies randomized meeting certain criteria.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

When looking at the studies evaluating gender reassignment surgery for patients with gender dysphoria, we found an array of disparate research designs. Most of the studies were conducted in Europe. Only six studies took place in the U.S. (Ainsworth, Spiegel, 2010; Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006; Lawrence, 2006; Leinung et al., 2013). Most of the studies that evaluated gender dysphoria were descriptive in nature; few made inferences which may be applicable to the Medicare population.

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions. CMS also explored the relative roles that psychological support, mental health care, cross-sex hormonal therapy, and the various gender reassignment related surgical procedures played in health outcomes.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as 1 study (Udeze et al., 2008; Megeri, Khoosal, 2007). For another publication, the complete manuscript could not be located despite an exhaustive search by the Library of Medicine (Barrett, 1998). This precluded adequate review, thus, it was not included. A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study.

The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

The studies in Figure 1 are categorized into 3 groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only populations box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of mixed populations of patients not stratified by treatment and which included a spectrum of therapeutic interventions.

When looking at the totality of studies, they fell into the following research design groups:

a. Prospective, non-blinded, observational, cross-sectional studies with no concurrent controls

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery. The mean age for each of these cohorts was: 50 (no standard deviation [S.D.]) only reassignment surgery, 51 (no S.D.) only facial surgery, 49 (no S.D.) both types of surgery, and 46 (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than 1 year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within 1 standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within 1 standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality-of-life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single, unspecified, Belgian university specialty clinic. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89 ± 10.21 (female-to-male: 37.03 ± 8.51 ; male-to-female: 42.26 ± 10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metadoioplasty 8 (with 5 of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation 3.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61 ± 18.16 versus 71.9 ± 18.31 and 71.51 ± 16.40 versus 79.3 ± 16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3 ± 19.7 or mental health 73.7 ± 18.2 . None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality-of-life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metadoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality-of-life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al., Weyers et al., or Wierckx et al. is unknown.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

The investigators assessed general quality of life, sexual function, and body image from the prior 4 weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center, specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed 7 question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 participants. Analysis of the data revealed that the patient's average age was 43.1 ± 10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95 ± 10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46 ± 1.57 , desire 3.12 ± 1.47 , arousal 2.95 ± 2.17 , lubrication 2.39 ± 2.29 , orgasm 2.82 ± 2.29 , and pain 2.21 ± 2.46 . Though these numbers were reported in the study, data on test population controls were not provided. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

A *post hoc* exploration of the data was performed that revealed the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med.* 2011 Dec;8(12):3379-88. Epub 2011 Jun 23.

Wierckx et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with 3 self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic. Investigators used the Dutch version of the SF-36 with 36 questions, 8 subscales, and 2 domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self-designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were contacted; however, ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the 1 year window. The age of patients was: 30 ± 8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ± 8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oophorectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metoidioplasty ($n=9$; 18.4%), phalloplasty ($n=8$ after metoidioplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device ($n=32$; 65.3%). All had started hormonal therapy at least 2 years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1 ± 20.7 versus 71.9 ± 18.3 and 72.6 ± 19.2 versus 79.3 ± 16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those with participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

Post hoc assessments suggested that being in relationship or having undergone phalloplasty did not impact the scores of the SF-36 domains. Also this assessment suggested that for patients in a relationship, sexual satisfaction was related to "Vitality" scores. Finally this assessment suggested a relationship between sexual satisfaction and more frequent orgasm and pleasure with the partner.

Salvador J, Massuda R, Andrezza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Salvador et al. conducted a prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 52 patients agreed to participate in the study. The age at follow-up was 36.3 ± 8.9 (range 15-58) years with the time to follow-up being 3.8 ± 1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304.

Blanchard et al. conducted a prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least 1 year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using the Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R).

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically ($p=0.01$). Additional surgeries in female-to-male patients included: oophorectomy/hysterectomy 92.1% and phalloplasty 7.9%. Additional procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation 53.1%. Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis 100% and breast implantation 33.3%. The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all 3 patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 63.2% of female-to-male patients cohabitated with partners of their natal gender. 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (1 female-to-male; 1 male-to-female with male partner preference; 3 male-to-female with female partner preference) indicated that they probably would undertake the surgery again. *Post hoc* analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec;34(6):515-7.

Tsoi conducted a prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigators assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥ 6 months, and willingness to function in the life of the desired gender for ≥ 6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 were female-to-male (44.4%) and 45 were male-to-female (55.6%) (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4 ± 4.4 (range 14-36) and 27.4 ± 4.0 ; (range 14-36); male-to-female 22.9 ± 4.6 (range 14-36) and 24.7 ± 4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p < 0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1 ± 8.0 . HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87 ± 9.15 (range 15-61). The current age of patients using hormones was 33.6 ± 9.1 ($n=120$) and older than the age of patients without hormone treatment (25.9 ± 7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6 ± 8.1 .

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female; ratio 1:1.7. The number of patients not on hormones and who had undergone at least 1 gender-related surgical procedure (genital or non-genital) was small ($n=2$). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was borderline elevated and consistent with a possible mood disorder in patients not using hormones. The mean scores for HAD-Anxiety, HAD-Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population $\pm$ non-genital reassignment surgery. The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center, specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but NOT genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty).

The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL-BREF) was used to evaluate quality-of-life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

Of the 277 patients recruited, 260 (93.9%) agreed to participate. Of this number, 193 were included in the study (the mean age of this group was 31.2 ± 9.9 (range 16-67)). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients; ratio 1:1.6. 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy $n=19$ (25.7%); mastectomy $n=29$ (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least 1 non-genital surgical procedure with mammoplasty augmentation being the most common procedure, $n=47$ (39.5%), followed by facial feminization, $n=11$ (9.2%), buttocks feminization, $n=9$ (7.6%), and vocal feminization (thyroid chondroplasty), $n=2$ (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81 ± 14.89 (range 12.50-96.88), "Physical" 63.51 ± 17.79 (range 14.29-100), "Psychological" 56.09 ± 16.27 (range 16.67-56.09), "Social" 60.35 ± 21.88 (range 8.33-100), and "Global QOL and Health" 55.44 ± 27.18 (range 0-100). The mean APGAR family score was 7.23 ± 2.86 (range 0-10).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all 4 domains and the general health and quality-of-life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, like age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry. 1988 Apr;152:550-3.

psychological tests (1 with some normative data). Concurrent controls were used in the study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients. The mean ages of the three cohorts were as follows: undergoing evaluation: mean age 34 years; wait-listed: mean age 35 years; and post-operative: mean age 37 years. Of the groups under evaluation or postsurgical, 16% (8 each) were unemployed; 8% of the waited listed patients were unemployed. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, and 14% of the same respective cohorts had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were relatively higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were lower in the post-operative cohort than in the other 2 cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with a self-designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery. Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; 8 (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their gender orientation; 13 (26%) declined to answer the question; 44 (27 [61.3%] female-to-male and 17 [38.6%] male-to-female) were unmarried or without a steady partner; 19 (38.0%) female-to-male patients reported the absence of a sex life (28.0% declined to answer this particular question); 15 (30%) male-to-female reported dissatisfaction with their sex lives. Additionally, 3 (6.0%) reported absence of sexual activity post-operatively. Ten (11.1%) were dissatisfied with their life situation (17.8% declined to answer this question). The study found that 2 female-to-male patients and 2 male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2 ± 10.3 . Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

The HADS test revealed non-pathologic results for depression (female-to-male: 6.64 ± 5.03 ; male-to-female: 6.58 ± 4.21) and borderline results for anxiety (female-to-male: 7.09 ± 5.11 ; male-to-female: 7.74 ± 6.13 , where a result of 7-10 = possible disorder). There were no differences by natal gender. HADS scores were missing for at least 1 person. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

b. Prospective, non-blinded, observational, cross-sectional studies with patients serving as their own controls

Rakic Z, Starcevic V, Maric J, Kelin K. *The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes.* Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator-designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least 6 months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least 1 year. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 32 participated in the study 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ± 13.4 months (range 6 months to 4 years). The age was female-to-male 27.8 ± 5.2 (range 23-37) and male-to-female 26.4 ± 7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and 8 (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery. Fifty percent of female-to-male and 54.5% of male-to-female patients reported being either unemployed or not being a student full-time prior to surgery. After surgery, no female-to-male patients and 7 (31.8%) male-to-female patients reported being either unemployed or not being a student full-time. The change was due to student status. Six (60%) of female-to-male patients and 15 (68.2%) of male-to-female patients reported being unemployed before and after surgery.

c. Prospective, non-blinded, observational, cross-sectional studies with controls

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation. The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 (range 29-67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without gender reassignment surgery [GRS]), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50 ± 10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria by surgical status. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post-surgical cohorts. The investigators assessed body image, and patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Körpers (FBek) which contained 3 domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0 ± 11.3 years; post-operative 38.2 ± 9.0 years. The mean duration after reassignment surgery was 51 ± 25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0 ± 3.8 versus 5.1 ± 3.7 ; male-to-female 8.1 ± 4.5 versus 4.7 ± 3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1 ± 2.9 versus 8.9 ± 3.1 ; male-to-female 7.0 ± 2.9 vs 9.5 ± 2.6 . Scores for insecurity and self-confidence in the post-operative cohort were not inferior to the normative values. Insecurity decreased statistically from 9.0 ± 3.8 in the female-to-male pre-operative cohort and from 8.1 ± 4.5 in the male-to-female pre-operative cohort to 4.4 ± 3.8 and 3.4 ± 2.3 in the respective post-operative cohorts. Self-confidence increased statistically from 3.1 ± 2.9 in the female-to-male pre-operative cohort and 7.0 ± 2.9 male-to-female pre-operative cohort to 9.29 ± 1.98 and 10.29 ± 2.0 in the respective post-operative cohorts.

d. Prospective, non-blinded, observational, cross-sectional studies with semi-matched controls

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinics, and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality-of-life assessment tools included a VAS and the King's Health Questionnaire (KHQ) with its eight domains including one for incontinence. The KHQ questionnaire and the numerical change/difference required for clinical significance (≥ 5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of the study was 51 years (range 39-62 years). The patients had undergone a median of 9 surgical procedures in comparison to the 2 undergone by controls. Patients were less likely to be married (23.6% versus 65%; $p=0.002$), and partnership status was unknown in 5 patients. The scores of VAS global satisfaction (maximal score 8) were lower for surgically reassigned patients (4.49 ± 0.1 SEM) than controls (7.35 ± 0.26 SEM) ($p < 0.0001$).

There were statistically and biologically significant differences for 4 of the 8 domains between the patients and controls: physical limitation: 37.6 ± 2.3 versus 20.9 ± 1.9 ($p < 0.0001$), personal limitation: 20.9 ± 1.9 versus 11.6 ± 0.4 ($p < 0.001$), role limitation: 27.8 ± 2.4 versus 34.6 ± 1.7 ($p < 0.5$), and general health: 31.7 ± 2.2 versus 41.0 ± 2.3 ($p < 0.02$). Information as to whether a high or low score was positive for the various domains was not provided. Wording from the abstract suggests that these 4 differences all reflected lower quality-of-life.

e. Prospective, blinded, observational, cross-sectional studies with no concurrent controls

Hess J, Rossi Neto R, Panic L, Rübber H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801.

Hess et al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic. Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire survey with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44 ± 9 (range 18-70) years and mean duration after surgery was 3 ± 1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality-of-life (QOL) was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed longer ago; whereas, more satisfaction with vaginal depth and width was present in more recent surgeries.

f. Prospective, non-blinded, observational, longitudinal and patients served as their own controls

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with 8 subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% rates the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3 ± 32.4 . The respective scores for the various gender dysphoric cohorts were 157.7 ± 49.8 at initial presentation, 119.7 ± 32.1 after hormone therapy, and 127.9 ± 37.2 after surgery. The scores for the general

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005 Jan;35(1):89-99.

Smith et al. conducted a prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigator assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post-surgery data were acquired at least 1 year post reassignment surgery.

The size of the pool of available patients was not identified. Overall 325 consecutive adolescents and adults initially were "involved." Of these, 103 (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy. After discontinuation of hormone therapy, the study was limited to adults. Of adults, 162 (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing. SCL global scores for psycho-neuroticism were minimally elevated before surgery 143.0 ± 40.7 (scoring range 90 to 450) and normalized after surgery 120.3 ± 31.4 . (An analysis using patient level data for only the completers was not conducted.)

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed) and Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed)

Udeze et al. conducted a prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within 6 months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33 ± 13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. A statistical trend in the anger/hostility subscale was reported. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16(6):511-22.

Kockott and Fahrner conducted a prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality,

transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument was not otherwise described in the publication or in other citations. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5 ± 13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7 ± 10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3 ± 9.4 years. The age of the patients who were no longer interested in surgery was 31.8 ± 6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score *within* each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences *between* groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least 1 year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive 2 to 4 hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score.

The clinic opened with 100 patients, but in follow-up, 52 of the 100 patients were interviewed and 50 of the interviewees gave consent for publication. Of these, 15 (4 female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (1 female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (5 female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 8% had some type of later psychiatric contact, which was approximately 3.5 times higher in those who had not undergone surgery or who had done so later. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. Both the absolute score value at follow-up and the magnitude of change were the same. By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere.

h. Prospective, non-blinded, observational, semi-cross sectional with no controls

Johansson et al. conducted non-blinded, observational study using a semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. No other information regarding the sites of care was provided. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥ 1 year of real-life experience in preferred gender, and ≥ 1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment 5 or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) 2 or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a 3 or 5 point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, there were 21 (35.0%) female-to-male and 39 (65%) male-to-female (ratio 1:1.9) ; 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including 1 post mastectomy), 5 were still in the process of completing surgery, and 5 (1 female-to-male; 4 male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The ages of the patients (ranges) at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22-49), and 38.9 (28-53) in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) in the male-to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p < 0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improvement in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to-female patients. A ≥ 5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these

patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=1), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38%) (41% of female- to-male; 36% of male-to-female) were reported to have a partner. Yet more than that number commented on partner relationships: 62.2 % of the 37 who answered (50.0% of female- to-male; 69.6% of male-to-female) reported improved partner relationships (5 [11.9%] declined to answer.); 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification.

In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers; 44.7 % of the 38 who answered (53.3% of female-to-male; 39.1% of male-to-female) reported improved work circumstances (4 [9.5%] declined to answer.); 61.9% were students or employed. The remainder (38.1%) were living on disability pensions (28.6%), unemployed (4.8%), or retired (4.8%).

i. Prospective, cross sectional, observational, internet self- report survey, with unknown blinding, no formal controls

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed, population with and without reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the SF-36 Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the 8 domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple

Printed on 7/25/2016. Page 33 of 145

A total of 379 U.S. respondents classified themselves as males or females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6 ± 10.8 years. 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. 254 (67.0%) reported any testosterone use in the past or currently; and 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery. The Physical Summary Score (53.45 ± 9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was within 1 standard deviation of the normative mean. The Mental Summary Score (39.63 ± 12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was well within 2 standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12 ± 10.2), Role Emotional (42.42 ± 11.6), Social Functioning (43.14 ± 10.9), and Vitality (46.22 ± 9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within 1 standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22 ± 11.9) than those with "No Testosterone Usage" (36.08 ± 12.6) ($p = 0.001$). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21 ± 11.6) and those without "Top Surgery" (38.01 ± 12.5) ($p = 0.067$). These differences were well within 1 standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

j. Partially prospective, non-blinded, observational studies with longitudinal designs and patients served as their own controls

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfäfflin conducted a partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the

Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Fribourg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results.

Overall, 140 patients received recruitment letters then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2 ± 5.78 years female-to-male and 52.9 ± 10.82 years male-to-female 52.9 ± 10.82 years. The intervals for follow-up were 14.1 ± 1.97 years and 13.7 ± 2.17 years respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oophorectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty; 94.3% of male-to-female patients had undergone vaginoplasty and perhaps an additional procedure (breast amplification, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35 ± 0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not in a steady relationship. Regular sexual relationships were reported by 57.1% of 35/36 female-to-male respondents and 39.4% of 33/35 of male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was large only for the "Life Satisfaction" scale. Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female-to-male patients and 19 of 35 male-to-female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

k. Partially prospective, non-blinded, observational studies with cross-sectional designs that had control groups but were not concurrent

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dan conducted a partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by 2 senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre-surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post-surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34 ± 9.5 years and female-to-male 33.3 ± 10.0 years. The other control group consisted of patients with personality disorder. 101 (27 men (33.9 ± 7.3 years) and 74 women (31.6 ± 8.2)) were tested during a treatment program. One year later, 98% were evaluated.

A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post- reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7 ± 1 . The Global Assessment of Function was higher (better) in the gender dysphoric groups 78.0 ± 8.9 than in the personality disorder cohort (53.0 ± 9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67 ± 0.57 and 0.56 ± 0.45 . Although they were nominally higher than the healthy normative controls (males: 0.32 ± 0.36 and females 0.41 ± 0.43), they were well within the non-pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

I. Partially prospective, non-blinded, observational studies with cross-sectional designs that had no control groups

Leinung et al. conducted a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p < 0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to-male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (> 32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (> 32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients. Of participants 36.4% were employed in jobs requiring a high school degree or less; 28.1% (excluding students) were on disability and/or unemployed. Rates of disability and unemployment were higher in male-to-female patients (31.8%) than female-to-male patients (14.0%). Mental health diagnoses reportedly were the major reason for disability. HIV infection and substance abuse were higher in male-to-female patients than female-to-male patients (8.3% versus 0% and 12.5% versus 6.0% respectively).

m. Retrospective, non-blinded, observational, longitudinal studies

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design of population treated with hormones, as well as, reassignment surgery and a population-based cohort. The investigators assessed mortality in patients who (a) were from a single-center, unspecified, university specialty clinic, (b) initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed by the clinic for at least 1 year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population was obtained through by the Central Bureau of Statistics of the Netherlands. Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio 1:2.4; $p < 0.0001$). The mean age at the time of hormone initiation in female-to-male and male-to-female patients was young: 26.1 ± 7.6 (range 16–56) years and 31.4 ± 11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p < 0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8 ± 6.3 and 19.4 ± 7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy as well as reassignment surgery. Of the patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI] 1.47-1.55) for males-to-females when compared to females in the general Dutch population. The small increase in all-cause mortality (12%) for females-to-males when compared to males in the general Dutch population was not statistically significant; 95% CI 0.87-1.42.

The major known contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide ($n=17$, SMR 5.70 [95% CI 4.93-6.54]), AIDS ($n=16$, SMR 30.20 [95% CI 26.0-34.7]), and illicit drug use ($n=5$, SMR 13.20 [95% CI 9.70-17.6]). An additional major contributor was “unknown cause” ($n=21$, SMR 4.00 [95% CI 3.52-4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and 6 (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients in older patients ($n=18$, SMR 1.64 [95% CI 1.43-1.87], mean age [range]: 59.7 [42-79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28-7.63], $p=0.01$). There was a smaller, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Although overall mortality was not increased in the hormone-treated female-to-male patients, there were more deaths due to illicit drug use than expected (SMR 25 [6.00-32.5]).

n. Retrospective, non-blinded, observational, longitudinal studies using matched national data

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were not delineated, but included evaluation and treatment by one of 6 specialized teams, name change, a new national identity number, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided. There were 804 patients identified with gender identity disorder (or related disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3±8.7 (range 20–62) and 36.3± 10.1 (range 21–69) respectively. Immigrant status was two times higher in reassigned patients (n=70, 21.6%) than in either type of control (birth [natal] sex matched n=294 [9.1%] or reassigned gender matched n=264 [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients (n=151 [57.8%]) than in either type of control (birth sex matched n=1,725 [61.5%] or reassigned gender matched n=1804 [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients (n=58, 17.9%) than in either type of control (birth sex matched n=123 [3.8%] or reassigned gender matched n=114 [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery (n=27 [8.3%]) than in controls (hazard ratio 2.8 [1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. The major contributor to this mortality difference was completed suicide (n=10 [3.1%]; adjusted hazard ratio 19.1 [5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients (n=9 [2.8%]) than in controls (hazard ratio 2.5 [1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery (n= 29 [9.0%] than in controls (adjusted hazard ratio 4.9 [2.9–8.5]). Male- to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons n= 64 [20.0%] than in controls (hazard ratio 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control. The increased risk for conviction of any crime or violent crime observed during the 1973-1988 interval was not seen later.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landen et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with “regret” in a national database. This same group (Landen et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra-group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least 1 year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After 2 years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures. (Dhejne et al., 2011) Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real-life experience phase, and family support.

Of the 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6]. The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.7% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. (This number [6.0%] appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense [usually in Thailand or the U.S.]. This cohort includes one person who was denied reassignment surgery by Sweden.)

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex-reassignment surgery outside of Sweden (36 of 41 after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male: male-to-female ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger than the entire female-to-male cohort (median age 22 versus 27 years) while the male-to-female applicants for reversal were older than the entire male-to-female cohort (median age 35 versus 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landen et al. extracted data from medical records and government verdicts. Logistic regression analyses were used identify relationships between variables. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different (albeit without Bonferroni correction) between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables has a more than additive effect.

The nationwide mortality studies by Dhejne et al. 2011 includes much, if not all, of the Landen (1998) patient population and most of the Dhejne (2014) population.

o. Randomized, non-blinded, longitudinal, some patients served as their own controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole et al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic. Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥ 2 year desire to change gender, a ≥ 1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at 6 months for diagnostic confirmation and exclusion of psychosis. Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity. The mean age and range of the entire cohort was 32.5 years (21-53).

Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms. Over the 2 year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic range for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior 2 years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct

statistical studies to compare the differences between the 2 cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities. Work status remained the same for post-operative patients which unemployment increased in the standard wait pre-operative cohort.

2. External Technology Assessments

- a.** CMS did not request an external technology assessment (TA) on this issue.
- b.** There were no AHRQ reviews on this topic.
- c.** There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.
- d.** There were two publications in the COCHRANE database, and both were tangentially related.

Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.

Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations
Boehmer U. *Am J Public Health*. 2002; 92: 1125-30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

f. There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. *NZHTA Report*. February 2002;1(1).
http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following: (1) Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists? And (2) If there is evidence of effectiveness, what subgroups would benefit from GRS?" Based upon the research, "Some 593 possibly relevant articles in abstract form were identified of which 70 articles were retrieved in full text."

The NZHTA stated, "The reviewed studies may indicate that early, rather than delayed, sex reassignment surgery is of greater benefit to transsexual people who have gone through rigorous assessment procedures and have been accepted for surgery. Also, the reviewed studies identify characteristics of groups defined as core and non-core transsexual people, but these characteristics are heterogeneous and anecdotal."

The NZHTA also stated, "Gender reassignment surgery may benefit some carefully assessed and selected transsexual people who have satisfied recognized diagnostic and eligibility criteria, and have received recognized standards of care for surgery. More research is required to improve the evidence base identifying the subgroups of transsexual people most likely to benefit from sex reassignment surgery."

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document:

Health Care for Transgender Individuals: Committee Opinion

Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gynecol. 2011;118:1454-8.

“Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient.”

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder
Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR,
Tompkins DA. *Arch Sex Behav.* 2012; 41:759–96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RCTs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. *J Clin Endocrinol Metab.* 2009;94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K. www.wpath.org/files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf *Int J Transgend.* 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

The SOC were carefully reviewed because they are frequently cited as the basis of management by clinicians, including some of the clinical groups with whom CMS spoke used it as a flexible guide. In the WPATH's SOC Appendix D titled "Evidence for Clinical Outcomes of Therapeutic Approaches," WPATH noted, "One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective." They further reported, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria."

e. American Psychological Association

Suggested citation until formally published in the *American Psychologist*: American Psychological Association. (2015):

Guidelines for Psychological Practice with Transgender and Gender Nonconforming People

Adopted by the Council of Representatives, August 5 & 7, 2015.

www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and transaffirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. <http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx>

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LGBT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(I)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies took place in a or suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as "clients" instead of "patients," and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire (8) and how, in some instances, with hormone treatment for gender dysphoria, the depression lessens.

8. Public Comments

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups. All of the initial public comments are available at:

<https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n&bc=ACAAAAAAgAAAA%3d%3d&>

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.” *Heckler v. Ringer*, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section of the proposed decision provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

A. Analysis

1. Study Demographics

These studies were conducted in a total of 15 countries. Most were conducted in Europe (a total of 24 in Europe: Belgium four, Germany four, Holland two, Norway one, Spain two, Sweden four, Switzerland three, the United Kingdom three [not including the Barrett, 1998 study and the duplicative Megeri, Khoosal, 2007 study], and Yugoslavia one). One was in Asia (Singapore); one in South America (Brazil). Seven were conducted in North America (U.S. six, Canada one). One of the North American studies was a U.S.-conducted internet survey with non-U.S. and U.S. participants with a sub-analysis of the U.S. patients (Newfield et al., 2006).

All of the studies, with the exception of a national-wide mortality study (Dhejne et al., 2011), the international internet survey (Newfield et al., 2006), and the internet/convention site survey (Ainsworth, Spiegel, 2010), were conducted with patient populations from single sites. Many of these clinical centers cited in these studies were specialized tertiary referral centers offering comprehensive, integrated (psychiatric-psychological, endocrine, and surgical) care and whose staff could have been involved in both the patient care and the study. Of the studies reviewed, the Lawrence, 2006 study was conducted by a physician psychologist who surveyed the patient population of a single U.S. surgeon. The Ainsworth, Spiegel, 2010 study was conducted by a U.S. otolaryngologist with extensive surgery training who assessed the impact of facial feminization on transgender patients. The Hess et al. 2014 study was undertaken at a German university urologic specialty clinic. The Wolfradt, Neumann, 2001 study was conducted in Germany by a university otorhinolaryngologist and psychologist on patients who had undergone vocal cord surgery after reassignment surgery. The Rupp, Pfafflin 2015 study was undertaken by investigators who had seen the patients in a German forensic psychotherapy clinic.

2. Patient Population

Demographic assessments of the studies revealed that the mean ages of participants were in the 20s and 30s. (See Appendix C and Appendix D). Even when including standard deviation, most patients included in the study were under the age 60. Age of participants in the reviewed studies is important to assess generalizability to the Medicare population which is comprised predominantly of adults' age 65 years and older. While certain younger disabled adults are included in Medicare, generalizability of studies performed outside in the U.S. is likely reduced further since criteria to determine disability is unique to Medicare. When reporting ages of patients participating in studies, studies included mean age of population, but often failed to reveal standard deviation of the population. Most studies reported pre and post gender reassignment surgery ages, though some studies only reported post-surgery ages (Dehjne, 2011; Kuhn et al., 2009; Rakic et al., 1996; Rupp, Pfafflin, 2015; Udeze et al., 2008; Megeri, Khoosal, 2007; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993).

There was extensive lack of study participation and loss to follow-up in the published studies. (See Appendix C and Appendix G). This suggests that the population that seeks evaluation/treatment for gender dysphoria and/or applies for reassignment surgery is not the same population that undergoes reassignment surgery without hesitation or regret. The notable numbers of incomplete questionnaires similarly raises questions. This selection bias limits generalizability of any results.

3. Study Design

As noted earlier, a number of research designs were found when exploring the question, “Does gender reassignment surgery improve health outcomes for Medicare beneficiaries with gender dysphoria?” (See Appendix C). The vast majority of studies found were observational in nature though there was a single randomized trial (Mate-Kole et al., 1990) (see Figure 1). Two of the studies were blinded. (Hess, 2014; Lawrence, 2006) A total of 29 studies were not blinded. The blinding status of the two internet surveys is unknown (Ainsworth, Spiegel, 2010; Newfield et al., 2006).

Observational studies can be prospective, retrospective, or have components of both. But each observational study design has limitations, and may not be able to show the true association between gender/reassignment surgery and improved health outcomes. Limitations of observational studies include that they frequently generate unreliable findings, and they also generate bias; because of confounding, causal inferences cannot reliably be drawn. Thus these types of studies are limited in terms of evidentiary weight. Only a true experimental study (e.g., randomized clinical trial) has the potential to demonstrate a causal relationship between two factors.

In general, one of the advantages of prospective studies is that they could potentially help determine factors associated with improved outcomes due to their longitudinal observation over time, and the collection of results at regular time intervals minimizes recall error. However, retrospective studies have problems including: some key statistics cannot be measured, significant biases including selection bias, recall bias, and information bias may limit a retrospective study’s applicability. Another problem with retrospective studies is that the temporal relationship between variables is frequently difficult to assess. Finally, it is difficult to control exposure or outcome assessment in a retrospective study design.

Studies that use controls as part of its research design have higher evidentiary weight than studies that lack controls. That is because the use of controls can help to eliminate the possibility of confounding. But controls by themselves are no guarantee of complete validity. In terms of the use of controls in these studies that we evaluated some studies had no concurrent controls; some studies used control groups, but they were not concurrent; some studies used semi-matched controls; and in other studies patients served as their own controls.

Seventeen observational studies, of which 10 used longitudinal and 7 used cross-sectional study designs, had formal control groups. In this group of studies, the cross-sectional studies used various controls including healthy volunteers and patients with other disorders or treatments. In this same group of studies, the longitudinal studies used various controls including the patients as their own serial control, other treatment groups in addition to having patients serve as their own controls, and control cohorts derived from national databases. Among the longitudinal studies with used patients as their own controls, 4 used self-report test instruments that were validated in large populations. Of these 4, 1 had more than 100 subjects, self-reported and others, or other cohorts using either national data or national registries. Some observational studies included in this analysis had surgery-only populations and used no controls, or used indirect controls incorporating normative testing. The remainder of the observational studies had mixed populations that included surgical patients and patients using other treatments or patients treated with non-genital gender reassignment surgical procedures. The studies that included groups with mixed populations either had no controls, or used indirect controls (statistical methods included ANOVA, correlation, or regression).

Our review included 25 prospective studies. Of these prospective studies, two used a retrospective approach to acquire data for a single parameter (Eldh et al., 1997; Johansson et al., 2009); one prospective study used a retrospective approach to acquire data for several parameters (Ruppin, Pfafflin, 2015); and one study used a

prospective approach beginning in 2005, but used a retrospective approach for data accumulated prior to that year (Leinung et al., 2013).

We found three retrospective studies (Asscheman et al., 2011; Dhejne et al., 2011; Landen et al., 1998). One study had at least a partially retrospective component, but with insufficient information to determine whether any of the data were obtained prospectively (Haraldsen, Dahl, 2000).

There were 11 longitudinal studies (Asscheman et al., 2011; Dhejne et al., 2011; Heylens et al., 2014; Kockott, Fahrner, 1987; Landen et al., 1998; Mate-Kole et al., 1979; Rakic et al., 1996; Rupp, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Ten of the longitudinal studies occurred in the group of studies with a designated control group (all of the above with the exception of Asscheman et al., 2011). In seven of the 11 longitudinal studies, the patients served as their own control over time before and after surgery (Heylens et al., 2014; Kockott, Fahrner, 1987; Meyer, Reter, 1979; Rakic et al., 1996; Rupp, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008).

There were 19 cross-sectional studies (Ainworth, 2010; Haraldsen, Dahl, 2000; Beatrice, 1985; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993; Gómez-Gil et al., 2012; Hepp et al., 2005; Motmans et al., 2012; Newfield et al., 2006; Gómez-Gil et al., 2013; Johansson et al., 2009; Leinung et al., 2013). Of this number, two were cross-sectional with the exception of data collection for aspects of a single parameter that had occurred in the past (Eldh et al., 1997; Johansson et al., 2009), and one study asked participants to recall the status of a parameter prior to treatment (Wierckx et al., 2011a).

Seventeen of the studies had explicit control groups. Of the studies with explicit control groups, two studies derived controls from national databases (Dhejne et al., 2011 and 2014; Landen et al., 1998); five studies used the patients themselves as longitudinal controls (Heylens 2014a; Rakic et al. 1996; Rupp, Pfafflin, 2015; Smith et al., 2005a; Udeze et al., 2008; Megeri 2007); eight used various other controls (Ainsworth, Spiegel, 2010; Beatrice 1985; Haraldsen, Dahl, 2000; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988 and 1990; Wolfradt, Neumann, 2001); and two studies used both treatment-type cohorts and patients themselves as controls (Kockott, Fahrner, 1987; Meyer, Reter 1979).

A number of studies consisted of surgical series, but in these studies there were no concurrent controls (Wierckx et al., 2011; Salvador et al., 2012; Blanchard et al., 1985; Tsoi, 1993; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Weyers, 2009a). In three surgical series normative data from psychometric instruments were used as the control (Blanchard et al., 1985a; Weyers 2009a; Wierckx et al., 2011b). In five surgical series, controls were lacking (except for the use of serial employment data in the Eldh et al. 1997 study) (Eldh et al., 1997; Hess 2014; Lawrence 2006; Salvador 2012; Tsoi, 1993).

Patients underwent a variety of surgical interventions in five studies. There were no controls. The role of surgical

intervention was assessed indirectly post-hoc by statistical techniques (analysis of variance and regression) (Gomez-Gil et al., 2012 and 2014; Hepp et al., 2005; Motmans et al., 2011; Newfield et al., 2006).

As mentioned in previous paragraphs, some prospective studies included in this analysis were cross-sectional in nature, and consisted of treated cohorts using a normative test, or a treatment cohort along with volunteer healthy cohorts. However, as we have noted, cross-sectional studies also have their limitations, including inability to determine temporal relationship between exposure and outcome (lacks time element). In other words, findings noted in a cross-sectional design cannot be inferred, because only current health and exposure to interventions are being studied. Also measurement error is an issue. Longitudinal studies with controls are most appropriate for determining this relationship between exposure and outcomes.

Observational studies have limitations. The lack of blinding has the potential to interfere with patient reported outcomes, which by their nature are subjective. Observational studies are prone to selection bias. Patients who seek treatment may not be the same as those who complete treatment-particularly if there are serial steps in the treatment process. (See Appendix G) Cross-sectional studies are prone to confounding. The impact of a particular step in a multi-faceted treatment process cannot be ascertained. The lack of a control group does not permit attribution of any outcome change to a specific intervention. There were seven studies where the patients themselves serve as longitudinal controls. The lack of a control makes it difficult to assess the results because there is not another group to make comparisons.

4. Psychometric Measurement Tools

There is also myriad use of measurement tools to assess patients suffering with gender dysphoria. (See Appendix E for a list of Psychometric Measurement tools.)

Some of the domains addressed in psychometric measurement tools measure the degree of depression and anxiety, body imagery, quality of life, identity traits, general wellbeing, physical and psychological function, self-concept, and others. Some of these measurement tools have been validated for patients with this condition, while others have been validated for other medical conditions. Some of the measurement tools found in this assessment were self-developed and there is no mention of validity when trying to determine if the test reliably measures what it is intended to measure.

5. Study Endpoints

A wide variety of study endpoints were used. Endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Some of the endpoints included

patient reported quality of life (QOL) as manifest by psychometric testing, sense of well-being, body imagery, anxiety and depression, sexual function and satisfaction, and social function. Objective endpoints included employment status, psychiatric function, and morbidity and mortality as well as adverse events.

Thirty of the studies employed 31 psychometric tools or investigator designed self-report surveys. (See Appendix E) Twenty investigators designed their own measurement tools or modified those of others.

External information on test validity, the size/composition of the reference population(s), diagnostic cut-points, and scoring was often not available because it was unpublished, proprietary, or in a non-English language. Six of the instruments, all non-specific, (the European QOL Survey, MMPI, SF-36, SCL-90, TSCS, and WHO-QOL-BREF), appear to have substantive normative data for comparative scoring (i.e., reference populations (≥ 1000) and obtained through representative sampling). Although these tools had been validated in a reference population, none had been validated in populations with gender dysphoria. Furthermore the investigators did not provide diagnostic cut-points and did not pre-specify the magnitude of test score change or test score difference considered to be biologically significant so the clinical importance could not be easily ascertained.

Only four investigator groups used only these psychometric tools validated in other large populations as their test instrument (Beatrice, 1985; Haraldsen, Dahl, 2000; Motmans et al., 2012; Newfield et al., 2006). Nine investigator groups used a mix of psychometric tools validated in large normative populations, less well validated tools, and/or self-designed tools (Ainsworth, Spiegel, 2010; Blanchard et al., 1985a; Gomez-Gil et al., 2014; Heylens 2014a; Ruppín, Pfafflin, 2015; Smith et al., 2005a (Udeze et al., 2008; Megeri 2007; Weyers 2009a; Wierckx et al., 2011b). Nine investigators used self-designed tools as their only test instrument (Eldh et al., 1997; Hess 2014; Johansson et al., 2009; Kockott, Fahrner, 1987; Lawrence, 2006; Meyer, Reter 1979; Rakic 1996; Salvador 2012; Tsoi 1993). A single investigator did not use any type of testing tool and provided only descriptive statistics (Leinung et al., 2013).

Three studies reported on complications linked or possibly linked to hormone treatment (Asscheman et al., 2011; Dhejne et al., 2011; Leinung et al., 2013), six studies reported on complications from reassignment surgery (Eldh et al., 1997; Lawrence, 2006; Ruppín, Pfafflin, 2015; Smith et al., 2005; Weyers et al., 2009; Wierckx et al., 2011). One study reported on serious and formalized regret for undergoing reassignment surgery (Landen et al., 1998), and one study reported on a patient with suicidal ideation who requested phallus removal (Meyer, Reter, 1979). Others reported on less severe or less formalized levels of regret. Five studies reported on the treatment or diagnosis of psychiatric disease (Dhejne et al., 2011; Haraldsen, Dahl, 2000; Hepp et al., 2005; Landen et al., 1998; Leinung et al., 2013; Meyer, Reter, 1979; Ruppín, Pfafflin, 2015; Udeze et al., 2008). Two studies reported on the history of psychiatric disease in their patient populations (Matte-Kole, 1988; Matte Kole, 1990).

Four studies reported on suicide attempts (Dhejne et al., 2011; Eldh et al., 1997; Heylens et al., 2013; Kockott, Fahrner, 1987), two studies reported on the history of suicide attempts in their patient population (Matte-Kole, 1988; Matte Kole, 1990). Three studies reported on suicide, of which one of them occurred incidentally (Asscheman et al., 2011; Blanchard et al., 1985; Dhejne et al., 2011). Two studies also reported on mortality (Asscheman et al., 2011; Dhejne et al., 2011).

There was a great degree of inconsistency in endpoints. Also endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Endpoints lacked operational definitions thus making their applicability difficult. CMS is interested in knowing what patients diagnosed with gender dysphoria believe are important endpoints that should be studied.

Mortality and Regret as Endpoints

Certain kinds of objective outcomes can be assessed by other types of study designs-albeit somewhat less robust. These include mortality and regret (as manifest by request for surgical reversal) when the data are rigorously prospectively collected in a comprehensive registry for all patients who have met specified entry criteria and treatment criteria.

More specifically, Swedish investigators extracted data from registries at the National Board of Health and Welfare to which all patients seeking reassignment surgery or reversal of reassignment surgery must make formal application. In the initial 1998 study, of the 233 applicants for reassignment surgery between July 1972 and June 1992, 20 were denied surgery, and subsequently 13 (3.8%) surgical patients requested return to the natal sex (Landen et al., 1998). In the 2014 follow-up study, of the 767 applicants for reassignment surgery or a change in legal status after surgery between 1960-2010, 86 were denied, and subsequently 15 (2.2%) requested reversal to the natal gender (Dhejne et al., 2014). Although the data from the two studies are not directly comparable because of the much shorter follow-up period in the latter study and although the analyses also did not consider other possible expressions of regret including suicide, the studies suggest that the majority of highly vetted patients in a structured care system do not express regret as defined by a formal request for return to natal gender status (Dhejne et al., 2011). The study, however, cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions.

Swedish investigators also conducted the most comprehensive study with functional endpoints of the 33 studies reviewed. This study relied on compulsory national databases (Dhejne et al., 2011) tracked all patients who had undergone reassignment surgery (at a mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls from the general population. They identified both increased mortality and increased psychiatric hospitalization. The mortality was primarily due to completed suicides (19.1-fold greater), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in control Swedes even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the sex of the control. For the same reasons as delineated above, this study cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions. The finding of this study demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant even in highly vetted patients in a structured care system.

B. Discussion

The question addressed in this NCD is whether there is sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria.

Gender dysphoria by the latest and prior nomenclature is a state in which there is incongruence between the gender assigned at birth and the gender(s) with which the person identifies. This incongruence may result in varying degrees of discontent and distress. Satisfaction and quality-of-life are well recognized as "latent variables" (hypothetical constructs) which cannot be measured directly (Borsboom et al., 2003; Newsom, 2015). As such, observable entities are used to infer or approximate satisfaction and/or quality-of-life. It may be challenging to identify parameters that truly reflect the nature and the magnitude of dysphoria in the individual. This challenge is followed by the need to know to what extent a specific test measures that which it purports to measure (test validity) and whether repeat testing will yield a comparable answer (test reliability).

The investigators of the clinical research reviewed in this NCD have attempted to measure dysphoria levels by objective data elements and by use of various psychometric and function scales/surveys. The objective data elements include a number of variables such as employment, morbidity, and formal requests for surgical reversal.

The psychometric tools used to assess outcomes have limitations. Many of the instruments that are most specific for the condition were designed by the investigators themselves or by other investigators in the field. In addition, the relevant diagnostic cut-points for scores and changes in scores that are clinically significant should be delineated to permit adequate interpretation of test results. As such, these studies were not definitive in nature.

Other factors might impact the utility of a given test. Patients undergo serial evaluations and a sequence of treatments (Bockting et al., 2011). These other interventions may reduce internal validity of the test. The affirmation and support obtained in psychotherapy-psychiatric care, the adjustment confidence gained in real life cross-gender behavior, and/or the physical and mental changes from hormone therapy may be (an) alternative cause(s) of the findings. Several studies suggest that there is a major therapeutic benefit from hormone therapy (Colizzi et al., 2013; Gómez-Gil et al., 2011; Gorin-Lazard et al., 2011, 2013; Heylens et al., 2014; Dubois, 2012). Another suggests that there is therapeutic benefit from time in the preferred gender role without other intervention (Greenberg, Laurence, 1981). As such, results from cross-sectional studies may be misleading. None of the studies used adequately matched controls over time. We believe longitudinal studies with serial assessment of the same patients would provide more robust answers. We note that even from the results from the four studies in which patients served as their own controls and which used an instrument known to be validated in large populations were negative (i.e., there was no improvement in psychometric or quality of life outcomes when patients were tested just prior to and at some point after the reassignment surgical intervention). (Heylens, 2014; Ruppín, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Further, rigorous studies with the use of appropriate comparison patients could better clarify the specific benefits and harms of each of the interventions.

CMS reviewed and considered potential objective measures of function including mortality, psychiatric treatment, and attempted suicide. None of the longitudinal studies in which patients served as their own control, however, comprehensively tracked changes in these events as objective measures of function before and after surgery. Events such as suicide and institutionalization were mentioned incidentally when describing patients excluded from a follow-up study or during the study (Heylens et al., 2014; Ruppín, Pfafflin, 2015). Other times investigators tracked these functional outcomes (e.g., psychiatric out-patient treatment, psychiatric in-patient treatment, and substance abuse) for the most current prior year (Ruppín, Pfafflin, 2015).

The most comprehensive study with functional endpoints, the Swedish study that followed all patients who had undergone reassignment surgery (at mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls, identified increased mortality and increased psychiatric hospitalization (Dhejne et al., 2011). The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Unfortunately, the study was not constructed to assess the impact of gender reassignment *per se*. The finding of this study, again, demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant, because of its clinical importance, its persistence over the interval of data collection and the increase in risk over time for the individual.

1. Patient Care

Additional questions regarding the care of patients with gender dysphoria remain. The specific type(s) of gender/sex reassignment surgery (genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific surgical procedures under study. Furthermore, most studies did not assess specific surgical procedures except for technical aspects. Surgical techniques have changed significantly over the last 60 years (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations presented a general framework and guidance on the care of transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH noted: "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care acknowledged the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

The surgical expertise and care setting(s) required to improve health outcomes in adults with gender dysphoria remain(s) uncertain. The selection of a particular surgeon could become an important variable if subjective outcomes depend on functional surgical results (Ross 1989). Many of these procedures involve complicated gynecologic, urologic surgical techniques accompanied by significant risk (Goddard et al., 2007a; Kuhn et al., 2011; Lawrence, 2003; Leclerc et al., 2015; Rachlin, 1999; Rupp, Pfafflin, 2015). Most of the studies for reassignment surgery have been conducted in northern Europe at select centers with integrated care (psychological, psychiatric, endocrinologic, and surgical) in which there is sequential evaluation of patients for progressively more invasive interventions.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care was often the centers' main focus rather than

2. Generalizability

With the variability in the study participants, providers and settings, the generalizability of the studies reviewed to the Medicare population is unclear. Many of the studies are old since they were conducted more than 10 years ago. Many of the programs were single-site centers without replication elsewhere. Most of these studies were conducted outside of the U.S. with far different medical systems for treatment and follow-up. The study populations were young and without significant physical or psychiatric co-morbidity. As noted above psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landen et al., 1998).

For the above reasons, it is difficult to generalize these studies to the Medicare population.

3. Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. There are, however, many gaps in the evidentiary base. These gaps have been delineated because they represent areas in which patient care can be optimized and which are opportunities for much needed research.

The Institute of Medicine, the National Institutes of Health, and others have delineated many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps.

The currently available evidence has limitations:

- There were design deficiencies. All but one of the studies were observational in nature. All but two were non-blinded. The accompanying loss to follow-up suggests that there is selection bias and that the population that seeks treatment for gender dysphoria is not the same population that undergoes reassignment surgery without hesitation or regret.
- The psychometric and psychosocial function endpoints are not well validated.

- There were limitations of the psychosocial endpoints and of the data collection of other hard functional outcomes. Evidence on mortality and especially suicide was stronger. The mortality and psychiatric hospitalization rates even after vetting in highly structured programs are of concern.
- There are insufficient data to select optimal candidates for surgery.
- The results were inconsistent, but negative in the best studies, i.e., those that reduced confounding by testing patients prior to and after surgery and which used psychometric tests with some established validation in other large populations. (Atkins et al., 2004; Balshem et al., 2011; Chan, Altman, 2005; Deeks et al., 2003; Guyatt et al., 2008a-c; 2011a-e; Kunz, Oxman, 1998; Kunz et al., 2007 and 2011; Odgaard-Jensen et al., 2011).
- Data on reassignment surgery performed on geriatric patients or follow-up data in geriatric patients who had reassignment surgery in the distant past is anecdotal (Orel, 2014).

C. Health Disparities

Four studies included information on racial or ethnic background. The participants in the 3 U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

D. Summary

Based on a thorough review of the clinical evidence available at this time, there is not enough evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria. There were conflicting (inconsistent) study results – of the best designed studies, some reported benefits while others reported harms. The quality and strength of evidence were low due to the mostly observational study designs with no comparison groups, potential confounding and small sample sizes. Many studies that reported positive outcomes were exploratory type studies (case-series and case-control) with no confirmatory follow-up. Due in part to the generally younger and healthier study participants, the generalizability of the studies to the Medicare population is also unclear. Additional research is needed. This proposed conclusion is consistent with the West Midlands Health Technology Assessment Collaboration (2009) that reported “[f]urther research is needed but must use more sophisticated designs with comparison groups.” WPATH also noted the need for further research: “More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.” Further, as mentioned earlier, patient preference is an important aspect of any treatment. With that in mind, CMS is interested in knowing from the patients with gender dysphoria what is important to them as a result of a successful gender reassignment surgery.

Knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. The specific role for various surgical procedures is less well understood than the role of hormonal intervention. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines and operating under European medical management and regulatory structures. Standard psychometric tools need to be developed and tested in the patients with gender dysphoria to validly assess long term outcomes. As such, further evidence in this area would contribute to the question of whether gender reassignment surgery improves health outcomes in adults with gender dysphoria.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

X. Appendices

A. Appendix A

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 <i>Chapter: Psychosexual Disorders</i>	Trans-sexualism 302.5x [Gender Identity Disorder of Child-hood (302.6)]	Required A (cross- gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85
DSM III- Revised 1987 <i>TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence</i>	Trans-sexualism (TS) (302.50) [GID of C]	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1 ^o and 2 ^o sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans- sexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood , non- trans-sexual type, added			
DSM IV 1994 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex

DSM Version	Condition Name	Criteria	Criteria	Comments
			•e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex •Clinically significant distress or impairment in social, occupational, or other important areas of functioning	
DSM IV-Revised 2000 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder (Term transsexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 <i>Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders</i>	Gender Dysphoria (302.85)	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	•Marked discordance between natal 1^o and 2^o sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1^o and 2^o sex characteristics** •Marked desire to acquire 1^o and 2^o sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

DSM Version	Condition Name	Criteria	Criteria	Comments
			* or in young adolescents, the anticipated 2^o sex characteristics ** or in young adolescents, prevent the development of the anticipated 2^o sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: • Strong desire to be of the other gender or an insistence that one is of another gender. • Strong preference for cross-gender roles in make-believe play. • Strong preference for the toys, games, or activities of the other gender. • Strong preference for playmates of the other gender. • In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing • In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1^o=primary
2^o=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
 Non-randomized controlled trials
 Prospective cohort studies
 Retrospective case control studies
 Cross-sectional studies
 Surveillance studies (e.g., using registries or surveys)
 Consecutive case series
 Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	480 w GID who did not apply or were not approved for SRS were excluded	324	324 (100%)	-
Dhejne 2014 Landen	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 52 excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, & 16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1 & 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional		40	10 (25%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	Controlled	14 excluded for demographic matching reasons			The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender identity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional		119	119 (100%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.			Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results ¹⁰³ .
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal		1331	1177 (88.4%)	-

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No analysis by tx status	The number in the available patient pool was not specified.			
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference

B/C=because

BSRI=Bem Sex Role Inventory

F=Female

FP-R=Freiberg Personality Inventory

GD=Gender dysphoria

GID=Gender identity disorder

HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems

M=Male

NA=Not applicable

SCL-90=Symptom Checklist-90

SF-36=Short Form 36

GRS=Sex reassignment surgery

Tx=Treatment

W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery: 50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian

Author	Age (years, mean, S.D., range)	Gender	Race
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3±8.7 (20-62), M to F 36.3±10.1(21-69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landen	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7±4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M to F; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).		-

Author	Age (years, mean, S.D., range)	Gender	Caucasian
		W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio 1:1.6.	
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F to M: 27.8 (18–46), M to F 37.3 (21–60). Time of GRS: F to M: 31.4 (22–49), M to F 38.2 (22–57). Time of follow-up for post-GRS: F to M: 38.9 (28–53), M to F 46.0 (25–69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve <i>Smilkstein</i>	Published in 1978 Initial data: 152 families in the U.S. A “friends” component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory <i>Beck, Ward, Mendelson, Mock, & Erbaugh</i>	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. It is copyrighted and requires a fee for use
Bem Sex Role Inventory <i>Bem</i>	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire <i>Clement & Lowe</i>	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale <i>Lindgren & Pauly</i> <i>(Kuiper, Dutch adaptation 1991)</i>	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire)	Developed circa 1966 Manual published 1970

Instrument Name and Developer	Development and Validation Information
<i>Crown & Crisp</i>	Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey <i>Anderson, Mikulić, Vermeylen, Lyly-Yrjanainen, & Zigante,</i>	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index <i>Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen</i>	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Körpers <i>Strauss</i>	Published 1996 (German)
Freiberg Personality Inventory <i>Fahrenberg, Hampel, & Selg</i>	7 th edition published 2001, 8 th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" <i>Smith, van Goozen, Kuiper, & Cohen-Kettenis</i>	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale <i>Altstotter-Gleich</i>	Published 1989 (German)
General Health Questionnaire <i>Goldberg & Blackwell (initial study)</i> <i>Goldberg & Williams (manual)</i>	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale <i>Zigmond & Snaith</i>	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1 st 50 compared to 2 nd 50.
Inventory of Interpersonal Problems <i>Horowitz</i>	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psychotherapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire <i>Kelleher, Cardozo, Khullar, & Salvatore</i>	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory <i>Hathaway & McKinley</i>	Published in 1941 Updated in 1989 with new, larger, more diverse sample.

Instrument Name and Developer	Development and Validation Information
<i>Butcher, Dahlstrom, Graham, & Tellegen</i>	MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphilia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences <i>Wolfradt</i>	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" <i>Cohen-Kettenis & van Goozen</i>	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale <i>Rosenberg</i>	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 <i>RAND</i> <i>Ware & Sherbourne 1992</i> <i>McHorney, Ware, & Raczek 1993</i>	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale <i>Watson & Friend</i>	Initial publication in 1969 Requires permission for use
Social Support Scale <i>Van Tilburg 1988</i>	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire <i>Spielberger, Gorsuch, Lushene, Vagg, & Jacobs</i>	Current format published in 1983 Proprietary test
Symptom Checklist-90 <i>Derogatis, Lipman, Covi</i> <i>Derogatis & Cleary</i>	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale <i>Fitts & Warren</i>	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other information available. Requires qualification for use
Utrecht Gender Dysphoria Scale <i>Cohen-Kettenis & van Goozen</i>	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)

Instrument Name and Developer	Development and Validation Information
WHO-Quality of Life (abbreviated version) <i>Harper for WHO group</i>	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Criminality, Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landen	Yes	-	-	-	Includes demographics*	Criminality, Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS, STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscherman et al.	Yes	-	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2 nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Körpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 ($\pm$ R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.**Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets**

Author	Test	Patient and Data Loss	Results
Psychometric Test			
Heylens et al. Belgium 2014	SCL-90R	90 applicants for SRS were recruited. •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx. •12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical comorbidity, personal decision for no tx, or personal decision for only hormone tx. •1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. •1 (12.2% of initial recruits) had not yet received SRS by study close. 46 (51.1% of recruited) underwent serial evaluation •The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) missing data for another 1.1% to 11.1%.	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.
Ruppin,Pfafflin, Germany 2015	SCL-90R	The number in the available patient pool was not specified.	

Author	Test	Patient and Data Loss	Results
		140 received recruitment letters. •2 (1.4% of those with recruitment letters) had died. •1 (0.7%) was institutionalized. •5 (3.6%) were ill. •8 (5.7%) did not have time. •8 (5.7%) stated that GD was no longer an issue. •8 (5.7%) provided no reason. •28 (20.0%) declined further contact. •9 (6.4%) were lost to follow-up. 71 (50.7%) agreed to participate. •2 (1.4%) had not undergone SRS •The test was not completed by 9. missing data for another 6.4%.	At t=0, the "global severity index "SCL-90R score was 0.53 ± 0.49. At post-SRS follow-up the score had decreased to 0.28 ± 0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70 ± 0.67 at t=0 and 0.26 ± 0.34 post-SRS.
Smith et al. Holland 2005	MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. •103 (31.7%) were not eligible to start hormone tx & real-life experience. •34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. •36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0 ± 40.7. At post SRS-follow-up, the score had decreased to 120.3 ± 31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. •Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.

Author	Test	Patient and Data Loss	Results
			There were no statistically significant changes in the global score or for any of the subscales.
National Databases			
Dehjne Sweden 2011	Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. •480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. •All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9-8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0-3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landen et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. •All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID=NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery
Tx=Treatment [Back to Top](#)

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID: 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstötter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentität* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid-Technique as shown at the example of the assessment of gender identity], Verlag für empirische Pädagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients.* 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to-male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry.* 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel-Journel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 June;328(19):1490-4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA*. 2010 Summer-Fall;22(4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristoni J, Menggiola MC, Jannini EA, Manfell C, Corona G, Morandi M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res*. 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013 Mar;13(3):214-22. Epub 2012 Dec 21. PMID: 23260128.

Barlow DH, Abel GG, Blanchard EB. Gender identity change in transsexuals. Follow-up and replications. *Arch Gen Psychiatry*. 1979 Aug;36(9):1001-7. PMID: 464738.

Barrett J. (1998) *Psychological and social function before and after phalloplasty*. University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or *IJT*. 1998; 2:1 or <http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal.pdf>.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav*. 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav*. 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteve I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med*. 2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

cases]. *Handchir Mikrochir Plast Chir.* 2011 Aug;43(4):215-21. Epub 2011 Aug 11. PMID: 21837614.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis.* 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* .1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. *Fertil Steril.* 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril.* 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology.* 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg.* 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol.* 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheeran B, Smith L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav*. 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes*. 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, management* (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav*. 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry*. 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med*. 2011 Jun 30;364(26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow-up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25(3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health.* 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am.* 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med.* 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev*. 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics*. 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav*. 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)*. 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav*. 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth*. 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self-injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med*. 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol*. 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex*. 2006;51(3):53-69. PMID: 17135115.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res*. 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT. Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend*. 2011;13:165–232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from a household probability sample of adults. *Am J Public Health*. 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol*. 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women's souls: Personal narrative of Thailand's transgendered youth*. Routledge.

Costantino A, Cerpolini S, Alvisi S, Morselli P, Venturoli S, Meriggiola M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther*. 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148-53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry*. 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril*. 2010 Dec;94(7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav*. 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Elaut E, Heylens G, van Maele G, Selvaggi G, T'Sjoen G, Rubens R, Hoebeke R, Monstrey S. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *J Sexol*. 2006;15:126-33. (Not in PubMed)

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry*. 2007 Apr;22(3):137-41. Epub 2006 Dec 26. PMID: 17188846.

Trial Collaborative Group, European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess*. 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male-to-female transsexual after initiation of hormone therapy. *J Clin Neurosci*. 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull*. 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry*. 1974;7(0):79-110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol*. 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis*. 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gyneco*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186(2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Larsson W, Landén M. Long term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6(2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav*. 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol*. 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduyn T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*. 2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav*. 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol*. 2011 Jun;51(2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis*. 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan-Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub*. 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinić B, Barišić J, Djordjevic ML, Vujović S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal*. 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72(1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg*. 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20(6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikulić B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview*. EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrz M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work*. EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Fares WH. The 'availability' bias: underappreciated but with major potential implications. *Crit Care*. 2014 Mar 12;18(2):118. PMID: 25029621.

Ferring D, Filipp SH. Messung des Selbstwertgefühls: Befunde zu Reliabilität, Validität und Stabilität der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica*. 1996; 42: 284-292. German. (Not in PubMed)

Ferron P, Young S, Boulianne C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med*. 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry*. 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab*. 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexual surgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir*. 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res*. 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav*. 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl*. 2011 May;13(3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol*. 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev*. 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol*. 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril*. 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand*. 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165(4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNiel D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law*. 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int*. 2007 Sep;100(3):607-13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website:
<http://www.stat.berkeley.edu/users/hhuang/141C-2008.html>. Section Website:
<http://www.stat.berkeley.edu/users/mgoldman>.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeyer A, Salameo M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess*. 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Trilla A, Salameo M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav*. 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav*. 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salameo M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav*. 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salameo-Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salameo M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012 May;37(5):662-70. Epub 2011 Sep 19. PMID: 21937168.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salameo M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res*. 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res*. 2005;64 Suppl 2:31-6. PMID: 16286768.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia*. 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes*. 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol*. 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med*. 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia*. 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012 Feb;9(2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis*. 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict*. 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res*. 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol*. 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis*. 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment*. 1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonasate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav*. 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 3;336(7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652): 1049-51. Erratum in: *BMJ*. 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol*. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol*. 2011 Dec;64(12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex*. 2011;58(1):10-51. PMID: 21213174.

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery*. 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007 Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand*. 2000 Oct;102(4):276-81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13(4):364-8. PMID: 13463138.

Hathaway SR, Reynolds PC, Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt*. 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res*. 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry*. 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics/objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services. Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology*. 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel)*. 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand*. 1971;47(1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel)*. 1973;6(2):65-80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat*. 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21;(1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol*. 1988 Dec;56(6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci*. 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav*. 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav*. 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile intranssexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B-Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha-reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013.
<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. <http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf>.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex*. 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol*. 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS*. 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltan R, Kawachi I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med.* 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav.* 2010 Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal.* 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab.* 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co-morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hiort O, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav.* 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci.* 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics.* 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav*. 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child*. 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav*. 1987 Dec;16(6):511-22. PMID: 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav*. 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences*. Stanford, Calif.: Stanford University Press, 1966.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. *Psychopathology*. 2008;41(2):96-100. Epub 2007 Nov 23. PMID: 18033979.

Krege S, Bex A, Lümnen G, Rübben H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollver H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol*. 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hildebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol*. 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6. PMID: 18990387.

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5. DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician*. 2013 Oct 15;88(8):Online. PMID: 24364581.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res*. 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation*. 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet*. 2011 April 9;377: 1211. PMID:2 1481690.

Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand*. 1998 Apr;97(4):284-9. PMID: 9570489.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol*. 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav*. 1999 Dec;28(6):581-3. PMID: 10650442.

Lawrence A. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003 Aug;32(4):299-315. PMID: 12856892.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav.* 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav.* 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Arch Sex Behav.* 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract.* 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lief HI, Hubschman L. Orgasm in the postoperative transsexual. *Arch Sex Behav*. 1993 Apr;22(2):145-55. PMID: 8476334.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav*. 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand*. 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975 Nov;4(6):639-56. PMID: 1212093.

Lioudaki E, Ganotakis ES, Mikhailidis DP, Nair DR. The estrogenic burden on vascular risk in male-to-female transsexuals. *Curr Pharm Des*. 2010;16(34):3815-22. PMID: 21128891

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav*. 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav*. 1979 Sep;8(5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav*. 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess*. 1984 Oct;48(5):500-7. PMID: 6389823.

Lundström B, Pauly I, Wålinder J. Outcome of sex reassignment surgery. *Acta Psychiatr Scand*. 1984 Oct;70(4):289-94. PMID: 6388248.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev*. 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D, Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grütters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab*. 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Mataix-Cols D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav*. 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry*. 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry*. 1990 Aug;157:261-4. PMID: 2224377.

Maycock L, Kennedy H. Breast care in the transgender individual. *J Midwifery Womens Health*. 2014 Jan-Feb;59(1):74-81. Epub 2013 Nov 13. PMID: 24224502.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med*. 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database*. 2009. No.3. www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2009/LGBTHealth030409finalversion.pdf.

Medraś M, Józków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol*. 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy*. 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health*. 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med*. 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl*. 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):607-15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

D- Meyer JK. Clinical variants among applicants for sex reassignment. *Arch Sex Behav*. 1974 Nov;3(6):527-58. PMID: 4429437.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10(4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav*. 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Ansseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miles C, Green R, Hines M. Estrogen treatment effects on cognition, memory and mood in male-to-female transsexuals. *Horm Behav*. 2006 Dec;50(5):708-17. Epub 2006 Aug 1. PMID: 16884726.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics*. 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient-subjects. *J Med Ethics*. 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol*. 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg*. 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. Spanish.

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med*. 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav*. 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollner H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med*. 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care*. 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015*. (Portland State quantitative methods) www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med*. 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. *J Acquir Immune Defic Syndr*. 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health*. 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health*. 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

Odgaard-Jensen J, Vist GE, Tinnert A, Kunz R, Alt EA, Schunemann H, Briel M, Nordmann A, Pugno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2011 Apr 13;(4):MR000012. PMID: 21491415.

O'Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J*. 1981;50(1):46-9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res*. 2008 Jan 15;157(1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med*. 2011 Feb;165(2):171-6. PMID: 21300658.

Olsson SE, Jansson I, Moller A. Men as women. Experiences from five case after administrative, hormonal, and surgical treatment. *Nord J Psychiatry*. 1996;50(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav*. 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Arch Sex Behav*. 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr*. 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav*. 2011 Apr;15(3):674-82. PMID: 21604064.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex*. 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögenderfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to-male transsexuals. *J Sex Med*. 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res*. 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to-female transsexual persons. *J Voice*. 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology*. 2005 Jul;16(4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968 Nov;147(5):460-71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15(1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril*. 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med*. 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work*. 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues of utility and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 May 23;7:9. PMID: 22621419.

Phillips J, Frances A, Cerullo MA, Charuvaedyne J, Decker HS, First MB, Chae M, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a plurilogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims*. December 2009. <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf>.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To-Male Genital Reconstructive Surgery. *IJT*. 1999 Jul-Sept;3(3). (Not in PubMed) <http://www.symposion.com/ijt/ijt990302.htm>
<http://www.iiav.nl/eazines/web/ijt/97-03/numbers/symposion/ijt990302.htm>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res*. 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res*. 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J*. 1959 Dec 26; 2(5164): 1448-52. PMID: 14436154.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):*Trans-sexualism and Sex reassignment*. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res*. 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav*. 1999 Feb;28(1):71-89. PMID: 10097806.

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand*. 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav*. 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl*. 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav*. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health*. 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract*. 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18(88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193–236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carroll RA. New women: Sexological outcomes of male-to-female gender reassignment surgery. *JSET*. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg*. 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol*. 2011 May;8(5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol*. 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer*. 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law*. 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology*. 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT*. 2001 Jul-Sept; 5(3):20 pages.
http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev*. 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract*. 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract*. 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001
Printed on 7/25/2016. Page 133 of 145

Apr;40(4):472-81. PMID: 15842032.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res*. 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand*. 1981 May;63(5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand*. 1981 Jul;64(1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav*. 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

J Am Acad Child Adolesc Psychiatry. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):192-206 Epub 2010 Mar 29. PMID: 20347346.

Steinle K. Hormonal management of the female-to-male transgender patient. *Midwifery Women's Health*. 2011 May-Jun;56(3):293-302. PMID: 21535376.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav*. 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J*. 1972 Mar;68(3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat*. 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBek), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Stroumsa D. The state of transgender health care: policy, law, and medical frameworks. *Am J Public Health* . 2014 Mar;104(3):e31-8. Epub 2014 Jan 16. PMID: 24432926.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev*. 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills*. 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2004 Dec;19(6):301-12. PMID: 15724806.

Swaab DF, Garcia-Falgueras A. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Funct Neurol*. 2009 Jan-Mar;24(1):17-28. PMID: 19403051.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res*. 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res*. 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female-to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand*. 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman J. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry.* 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand.* 1988 Oct;78(4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J.* 1992 Apr;33(2):182-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J.* 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore.* 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess.* 1979. Aug;43(4):385-7. PMID: 383946.

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007 Oct;83(984):638-42. PMID: 17916872.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol*. 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol*. 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedeker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab*. 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsen I. T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierzak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med*. 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. *Arch Sex Behav*. 2015 Jul;44(5):1281-7. Epub 2015

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav*. 2013; 42:361-70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav*. 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med*. 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mirošević Marojević L, Nović M, Tandić Gajić M, Stojanović M, Marina L V, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal*. 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow- up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry*. 1978;132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Weigert R, Frison E, Sessieq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology*. 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quality of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people. Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV*. World Health Organization. July 2015. <http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/>.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*. 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van De Peer F, Dedeker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedeker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med*. 2012 Oct;9(10):2641-51. Epub 2012 Aug 20. PMID: 22906135.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

B-Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014 May;11(5):1240-7. Epub 2014 Mar 12. PMID: 24618412.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction*. 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health*. 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex*. 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S. The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract*. 1999; 49 (449): 991-2. PMID: 10824346.

Wilson RC, Nimkarn S, Dumic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic-specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. *Mol Genet Metab*. 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab*. 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect*. 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol*. 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav*. 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol*. 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav*. 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders*. (6th version) February, 2001.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr.* 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez-Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab.* 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals.* (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5 α -Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopoulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg.* 2006 May;77(5):432-8. German. Erratum in *Chirurg.* 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis.* 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry*. 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res*. 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901-14. PMID: 23868018.

[Back to Top](#)

EXHIBIT F

Proposed Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

[Back to Top](#)

Proposed Decision Memo

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Proposed Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: June 2, 2016

I. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance
APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Craps Experimental Index
CHIS - California Health Interview Survey
CI - Confidence Interval
CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Excerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Körpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King's Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale
SF - Short Form
SMR - Standardized Mortality Ratio
SOC - Standards of Care
STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
STAI-X2 - Spielberger State and Trait Anxiety Questionnaire

TSCS - Tennessee Self-Concept Scale

U.S. - United States

VAS - Visual Analog Scale

WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100

WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Therapeutic options for gender dysphoria include behavioral and psychotherapies, hormonal treatments, and a number of surgeries used for gender reassignment. This proposed decision is only focusing on gender reassignment surgery.

B. Prevalence of Gender Dysphoria

Prevalence of gender dysphoria estimates have been reported by several investigators.

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. The following states have at least 100 transgender beneficiaries: California, Florida, Georgia, Illinois, Massachusetts, Michigan, Minnesota, New York, Pennsylvania, Ohio, Texas, Washington, and Wisconsin. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. Of note, for the transgender population under age 65, the most prevalent chronic conditions were depression, major depressive affective disorder, and anxiety. Approximately 75% of transgender Medicare beneficiaries have been affected by depression, which is a disproportionately high amount compared to the Medicare population as a whole with 14% of Medicare fee-for-service beneficiaries suffering from the disease (CMS, *Chronic Conditions Among Medicare Beneficiaries*, 2012 at <https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/chronic-conditions/downloads/2012chartbook.pdf>). Based on the claims data, about 48% of transgender beneficiaries use hormone therapy, which are coverable under the Medicare Part D prescription drug benefit program (CMS Office of Minority Health (2015, June). New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. Paper presented at the Academy Health Annual Research Meeting, Minneapolis, Minnesota and Gay and Lesbian Medical Association Meeting, Portland, Oregon).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson, Moller 2003).

C. Interventions

Table 1 provides information about some of the types of therapeutic interventions for transgender individuals.

Table 1. Types of Therapeutic Intervention (May Not be Exhaustive)

Treatment Category	Male to Female	Female to Male
HORMONAL¹		
Core		
	Estrogens	Androgens Progestins/GnRH analogues for menses suppression as needed after 1 yr of androgens

Treatment Category	Male to Female	Female to Male
	Anti-androgens (e.g., spironolactone, 5- reductase blockers, androgen receptor blockers, GnRH analogues)	
SURGICAL^{2,3}		
Natal Internal Genital Removal	Orchidectomy (testes)	Hysterectomy (uterus) and Salpingo-oophorectomy (fallopian tubes + ovaries)
Natal External Genital Removal	Penectomy	NA
Breast Removal	NA	Mastectomy
Genital Reconstruction ²	Vaginoplasty Clitoroplasty Labiaplasty Urethrostomy	Metoidioplasty or Phalloplasty Inflatable/rigid penile prosthesis insertion Scrotal reconstruction

RH=gonadotropin releasing hormone NA=not applicable ?=possible =increased 2o=secondary

1—Bowman et al., 2012; Deutch, 2015; Elaut et al., 2010 Gooren et al., 2005 ,2013, and 2014; Heresova, 1986; Jacobeit, et al., 2009; Kronawitter et al., 2009; Meuller, 2010; Meyer et al., 1981; Pelusi et al., 2014; Schlatterer et al., 1998; Seal et al., 2012; Traish et al., 2010; Wierckx et al., 2011b, 2014; Williamson et al., 2010.

2—Revisions may be required. Kuhn et al., 2011.

3—Goddard et al., 2007a; Jain, Bradbeer, 2007; Selvaggi, Bellringer, 2011; Wroblewski et al., 2013.

III. History of Medicare Coverage

CMS does not currently have an NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a national coverage analysis (NCA) for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A)

Under §1832 (Scope of Part B)

Under §1861(s) (Definition of Medical and Other Health Services)

Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Table 2: Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
August 1, 1989	The Health Care Financing Agency (HCFA; predecessor agency to CMS) published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.
December 3, 2015	CMS accepts an external request to open an NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.

V. FDA Status

Surgical procedures *per se* are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved/cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

Public commenters sometimes cite the published clinical evidence and provide CMS with useful information. Public comments that provide information based on unpublished evidence, such as the results of individual practitioners or patients, are less rigorous and, therefore, less useful for making a coverage determination. CMS uses the initial comment period to inform the public of its proposed decision. CMS responds in detail to the public comments that were received in response to the proposed decision when it issues the final decision memorandum.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We considered articles cited by the requestor, in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies evaluating therapeutic interventions for gender dysphoria. There was particular emphasis on the various surgical interventions, but other treatments including hormone therapy, psychotherapy, psychiatric treatment, ancillary reproductive and gender modifying services, and post-operative surveillance services for natal sex organs were also included because of their serial and sometimes overlapping roles in patient management. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) AND/OR quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), employment status, relationships, other social function, suicide (attempts), mortality, sexual function, urinary function, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). That is because when evaluating patients with this condition most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early termination, completed, and ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. The CMS internal search was limited to articles published prior to March 21, 2016. CMS reviewed results of clinical trials involving adult human subjects; to reports of prospective (e.g., blinded, non-blinded, cross sectional), partially prospective, retrospective longitudinal studies randomized meeting certain criteria.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

When looking at the studies evaluating gender reassignment surgery for patients with gender dysphoria, we found an array of disparate research designs. Most of the studies were conducted in Europe. Only six studies took place in the U.S. (Ainsworth, Spiegel, 2010; Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006; Lawrence, 2006; Leinung et al., 2013). Most of the studies that evaluated gender dysphoria were descriptive in nature; few made inferences which may be applicable to the Medicare population.

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions. CMS also explored the relative roles that psychological support, mental health care, cross-sex hormonal therapy, and the various gender reassignment related surgical procedures played in health outcomes.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as 1 study (Udeze et al., 2008; Megeri, Khoosal, 2007). For another publication, the complete manuscript could not be located despite an exhaustive search by the Library of Medicine (Barrett, 1998). This precluded adequate review, thus, it was not included. A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study.

The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

The studies in Figure 1 are categorized into 3 groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only populations box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of mixed populations of patients not stratified by treatment and which included a spectrum of therapeutic interventions.

When looking at the totality of studies, they fell into the following research design groups:

a. Prospective, non-blinded, observational, cross-sectional studies with no concurrent controls

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery. The mean age for each of these cohorts was: 50 (no standard deviation [S.D.]) only reassignment surgery, 51 (no S.D.) only facial surgery, 49 (no S.D.) both types of surgery, and 46 (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than 1 year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within 1 standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within 1 standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality-of-life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single, unspecified, Belgian university specialty clinic. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89 ± 10.21 (female-to-male: 37.03 ± 8.51 ; male-to-female: 42.26 ± 10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metadoioplasty 8 (with 5 of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation 3.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61 ± 18.16 versus 71.9 ± 18.31 and 71.51 ± 16.40 versus 79.3 ± 16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3 ± 19.7 or mental health 73.7 ± 18.2 . None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality-of-life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metadoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality-of-life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al., Weyers et al., or Wierckx et al. is unknown.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

The investigators assessed general quality of life, sexual function, and body image from the prior 4 weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center, specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed 7 question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 participants. Analysis of the data revealed that the patient's average age was 43.1 ± 10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95 ± 10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46 ± 1.57 , desire 3.12 ± 1.47 , arousal 2.95 ± 2.17 , lubrication 2.39 ± 2.29 , orgasm 2.82 ± 2.29 , and pain 2.21 ± 2.46 . Though these numbers were reported in the study, data on test population controls were not provided. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

A *post hoc* exploration of the data was performed that revealed the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med.* 2011 Dec;8(12):3379-88. Epub 2011 Jun 23.

Wierckx et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with 3 self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic. Investigators used the Dutch version of the SF-36 with 36 questions, 8 subscales, and 2 domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self-designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were contacted; however, ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the 1 year window. The age of patients was: 30 ± 8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ± 8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oophorectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metoidioplasty ($n=9$; 18.4%), phalloplasty ($n=8$ after metoidioplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device ($n=32$; 65.3%). All had started hormonal therapy at least 2 years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1 ± 20.7 versus 71.9 ± 18.3 and 72.6 ± 19.2 versus 79.3 ± 16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those with participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

Post hoc assessments suggested that being in relationship or having undergone phalloplasty did not impact the scores of the SF-36 domains. Also this assessment suggested that for patients in a relationship, sexual satisfaction was related to "Vitality" scores. Finally this assessment suggested a relationship between sexual satisfaction and more frequent orgasm and pleasure with the partner.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Salvador et al. conducted a prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 52 patients agreed to participate in the study. The age at follow-up was 36.3 ± 8.9 (range 15-58) years with the time to follow-up being 3.8 ± 1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304.

Blanchard et al. conducted a prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least 1 year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using the Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R).

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically ($p=0.01$). Additional surgeries in female-to-male patients included: oophorectomy/hysterectomy 92.1% and phalloplasty 7.9%. Additional procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation 53.1%. Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis 100% and breast implantation 33.3%. The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all 9 patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 63.2% of female-to-male patients cohabitated with partners of their natal gender. 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (1 female-to-male; 1 male-to-female with male partner preference; 3 male-to-female with female partner preference) indicated that they probably would undertake the surgery again. *Post hoc* analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec;34(6):515-7.

Tsoi conducted a prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigators assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥ 6 months, and willingness to function in the life of the desired gender for ≥ 6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 were female-to-male (44.4%) and 45 were male-to-female (55.6%) (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4 ± 4.4 (range 14-36) and 27.4 ± 4.0 ; (range 14-36); male-to-female 22.9 ± 4.6 (range 14-36) and 24.7 ± 4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p < 0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1 ± 8.0 . HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87 ± 9.15 (range 15-61). The current age of patients using hormones was 33.6 ± 9.1 ($n=120$) and older than the age of patients without hormone treatment (25.9 ± 7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6 ± 8.1 .

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female; ratio 1:1.7. The number of patients not on hormones and who had undergone at least 1 gender-related surgical procedure (genital or non-genital) was small ($n=2$). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was borderline elevated and consistent with a possible mood disorder in patients not using hormones. The mean scores for HAD-Anxiety, HAD-Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population $\pm$ non-genital reassignment surgery. The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center, specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but NOT genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty).

The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL-BREF) was used to evaluate quality-of-life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

Of the 277 patients recruited, 260 (93.9%) agreed to participate. Of this number, 193 were included in the study (the mean age of this group was 31.2 ± 9.9 (range 16-67)). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients; ratio 1:1.6. 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy $n=19$ (25.7%); mastectomy $n=29$ (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least 1 non-genital surgical procedure with mammoplasty augmentation being the most common procedure, $n=47$ (39.5%), followed by facial feminization, $n=11$ (9.2%), buttocks feminization, $n=9$ (7.6%), and vocal feminization (thyroid chondroplasty), $n=2$ (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81 ± 14.89 (range 12.50-96.88), "Physical" 63.51 ± 17.79 (range 14.29-100), "Psychological" 56.09 ± 16.27 (range 16.67-56.09), "Social" 60.35 ± 21.88 (range 8.33-100), and "Global QOL and Health" 55.44 ± 27.18 (range 0-100). The mean APGAR family score was 7.23 ± 2.86 (range 0-10).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all 4 domains and the general health and quality-of-life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, like age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry. 1988 Apr;152:550-3.

psychological tests (1 with some normative data). Concurrent controls were used in the study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients. The mean ages of the three cohorts were as follows: undergoing evaluation: mean age 34 years; wait-listed: mean age 35 years; and post-operative: mean age 37 years. Of the groups under evaluation or postsurgical, 16% (8 each) were unemployed; 8% of the waited listed patients were unemployed. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, and 14% of the same respective cohorts had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were relatively higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were lower in the post-operative cohort than in the other 2 cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with a self-designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery. Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; 8 (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their gender orientation; 13 (26%) declined to answer the question; 44 (27 [61.3%] female-to-male and 17 [38.6%] male-to-female) were unmarried or without a steady partner; 19 (38.0%) female-to-male patients reported the absence of a sex life (28.0% declined to answer this particular question); 15 (30%) male-to-female reported dissatisfaction with their sex lives. Additionally, 3 (6.0%) reported absence of sexual activity post-operatively. Ten (11.1%) were dissatisfied with their life situation (17.8% declined to answer this question). The study found that 2 female-to-male patients and 2 male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2 ± 10.3 . Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

The HADS test revealed non-pathologic results for depression (female-to-male: 6.64 ± 5.03 ; male-to-female: 6.58 ± 4.21) and borderline results for anxiety (female-to-male: 7.09 ± 5.11 ; male-to-female: 7.74 ± 6.13 , where a result of 7-10 = possible disorder). There were no differences by natal gender. HADS scores were missing for at least 1 person. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

b. Prospective, non-blinded, observational, cross-sectional studies with patients serving as their own controls

Rakic Z, Starcevic V, Maric J, Kelin K. *The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes.* Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator-designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least 6 months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least 1 year. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 32 participated in the study 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ± 13.4 months (range 6 months to 4 years). The age was female-to-male 27.8 ± 5.2 (range 23-37) and male-to-female 26.4 ± 7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and 8 (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery. Fifty percent of female-to-male and 54.5% of male-to-female patients reported being either unemployed or not being a student full-time prior to surgery. After surgery, no female-to-male patients and 7 (31.8%) male-to-female patients reported being either unemployed or not being a student full-time. The change was due to student status. Six (60%) of female-to-male patients and 15 (68.2%) of male-to-female patients reported being unemployed before and after surgery.

c. Prospective, non-blinded, observational, cross-sectional studies with controls

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation. The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 (range 29-67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without gender reassignment surgery [GRS]), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50 ± 10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria by surgical status. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post-surgical cohorts. The investigators assessed body image, and patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Körpers (FBek) which contained 3 domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0 ± 11.3 years; post-operative 38.2 ± 9.0 years. The mean duration after reassignment surgery was 51 ± 25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0 ± 3.8 versus 5.1 ± 3.7 ; male-to-female 8.1 ± 4.5 versus 4.7 ± 3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1 ± 2.9 versus 8.9 ± 3.1 ; male-to-female 7.0 ± 2.9 vs 9.5 ± 2.6 . Scores for insecurity and self-confidence in the post-operative cohort were not inferior to the normative values. Insecurity decreased statistically from 9.0 ± 3.8 in the female-to-male pre-operative cohort and from 8.1 ± 4.5 in the male-to-female pre-operative cohort to 4.4 ± 3.8 and 3.4 ± 2.3 in the respective post-operative cohorts. Self-confidence increased statistically from 3.1 ± 2.9 in the female-to-male pre-operative cohort and 7.0 ± 2.9 male-to-female pre-operative cohort to 9.29 ± 1.98 and 10.29 ± 2.0 in the respective post-operative cohorts.

d. Prospective, non-blinded, observational, cross-sectional studies with semi-matched controls

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinics, and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality-of-life assessment tools included a VAS and the King's Health Questionnaire (KHQ) with its eight domains including one for incontinence. The KHQ questionnaire and the numerical change/difference required for clinical significance (≥ 5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of the study was 51 years (range 39-62 years). The patients had undergone a median of 9 surgical procedures in comparison to the 2 undergone by controls. Patients were less likely to be married (23.6% versus 65%; $p=0.002$), and partnership status was unknown in 5 patients. The scores of VAS global satisfaction (maximal score 8) were lower for surgically reassigned patients (4.49 ± 0.1 SEM) than controls (7.35 ± 0.26 SEM) ($p<0.0001$).

There were statistically and biologically significant differences for 4 of the 8 domains between the patients and controls: physical limitation: 37.6 ± 2.3 versus 20.9 ± 1.9 ($p<0.0001$), personal limitation: 20.9 ± 1.9 versus 11.6 ± 0.4 ($p<0.001$), role limitation: 27.8 ± 2.4 versus 34.6 ± 1.7 ($p<0.5$), and general health: 31.7 ± 2.2 versus 41.0 ± 2.3 ($p<0.02$). Information as to whether a high or low score was positive for the various domains was not provided. Wording from the abstract suggests that these 4 differences all reflected lower quality-of-life.

e. Prospective, blinded, observational, cross-sectional studies with no concurrent controls

Hess J, Rossi Neto R, Panic L, Rübber H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801.

Hess et al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic. Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire survey with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44 ± 9 (range 18-70) years and mean duration after surgery was 3 ± 1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality-of-life (QOL) was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed longer ago; whereas, more satisfaction with vaginal depth and width was present in more recent surgeries.

f. Prospective, non-blinded, observational, longitudinal and patients served as their own controls

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with 8 subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% rates the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3 ± 32.4 . The respective scores for the various gender dysphoric cohorts were 157.7 ± 49.8 at initial presentation, 119.7 ± 32.1 after hormone therapy, and 127.9 ± 37.2 after surgery. The scores for the general

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005 Jan;35(1):89-99.

Smith et al. conducted a prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigator assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post-surgery data were acquired at least 1 year post reassignment surgery.

The size of the pool of available patients was not identified. Overall 325 consecutive adolescents and adults initially were "involved." Of these, 103 (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy. After discontinuation of hormone therapy, the study was limited to adults. Of adults, 162 (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing. SCL global scores for psycho-neuroticism were minimally elevated before surgery 143.0 ± 40.7 (scoring range 90 to 450) and normalized after surgery 120.3 ± 31.4 . (An analysis using patient level data for only the completers was not conducted.)

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed) and Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed)

Udeze et al. conducted a prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within 6 months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33 ± 13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. A statistical trend in the anger/hostility subscale was reported. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16(6):511-22.

Kockott and Fahrner conducted a prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality,

transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument was not otherwise described in the publication or in other citations. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5 ± 13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7 ± 10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3 ± 9.4 years. The age of the patients who were no longer interested in surgery was 31.8 ± 6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score *within* each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences *between* groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least 1 year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive 2 to 4 hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score.

The clinic opened with 100 patients, but in follow-up, 52 of the 100 patients were interviewed and 50 of the interviewees gave consent for publication. Of these, 15 (4 female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (1 female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (5 female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 8% had some type of later psychiatric contact, which was approximately 3.5 times higher in those who had not undergone surgery or who had done so later. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. Both the absolute score value at follow-up and the magnitude of change were the same. By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere.

h. Prospective, non-blinded, observational, semi-cross sectional with no controls

Johansson et al. conducted non-blinded, observational study using a semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. No other information regarding the sites of care was provided. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥ 1 year of real-life experience in preferred gender, and ≥ 1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment 5 or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) 2 or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a 3 or 5 point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, there were 21 (35.0%) female-to-male and 39 (65%) male-to-female (ratio 1:1.9) ; 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including 1 post mastectomy), 5 were still in the process of completing surgery, and 5 (1 female-to-male; 4 male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The ages of the patients (ranges) at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22-49), and 38.9 (28-53) in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) in the male-to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p < 0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improvement in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to-female patients. A ≥ 5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these

patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=1), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38%) (41% of female- to-male; 36% of male-to-female) were reported to have a partner. Yet more than that number commented on partner relationships: 62.2 % of the 37 who answered (50.0% of female- to-male; 69.6% of male-to-female) reported improved partner relationships (5 [11.9%] declined to answer.); 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification.

In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers; 44.7 % of the 38 who answered (53.3% of female-to-male; 39.1% of male-to-female) reported improved work circumstances (4 [9.5%] declined to answer.); 61.9% were students or employed. The remainder (38.1%) were living on disability pensions (28.6%), unemployed (4.8%), or retired (4.8%).

i. Prospective, cross sectional, observational, internet self- report survey, with unknown blinding, no formal controls

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed, population with and without reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the SF-36 Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the 8 domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple

Printed on 7/25/2016. Page 33 of 145

A total of 379 U.S. respondents classified themselves as males or females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6 ± 10.8 years. 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. 254 (67.0%) reported any testosterone use in the past or currently; and 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery. The Physical Summary Score (53.45 ± 9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was within 1 standard deviation of the normative mean. The Mental Summary Score (39.63 ± 12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was well within 2 standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12 ± 10.2), Role Emotional (42.42 ± 11.6), Social Functioning (43.14 ± 10.9), and Vitality (46.22 ± 9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within 1 standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22 ± 11.9) than those with "No Testosterone Usage" (36.08 ± 12.6) ($p = 0.001$). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21 ± 11.6) and those without "Top Surgery" (38.01 ± 12.5) ($p = 0.067$). These differences were well within 1 standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

j. Partially prospective, non-blinded, observational studies with longitudinal designs and patients served as their own controls

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfafflin conducted a partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the

Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Fribourg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results.

Overall, 140 patients received recruitment letters then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2 ± 5.78 years female-to-male and 52.9 ± 10.82 years male-to-female 52.9 ± 10.82 years. The intervals for follow-up were 14.1 ± 1.97 years and 13.7 ± 2.17 years respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oophorectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty; 94.3% of male-to-female patients had undergone vaginoplasty and perhaps an additional procedure (breast amplification, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35 ± 0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not in a steady relationship. Regular sexual relationships were reported by 57.1% of 35/36 female-to-male respondents and 39.4% of 33/35 of male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was large only for the "Life Satisfaction" scale. Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female-to-male patients and 19 of 35 male-to-female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

k. Partially prospective, non-blinded, observational studies with cross-sectional designs that had control groups but were not concurrent

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dan conducted a partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by 2 senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre-surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post-surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34 ± 9.5 years and female-to-male 33.3 ± 10.0 years. The other control group consisted of patients with personality disorder. 101 (27 men (33.9 ± 7.3 years) and 74 women (31.6 ± 8.2)) were tested during a treatment program. One year later, 98% were evaluated.

A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post- reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7 ± 1 . The Global Assessment of Function was higher (better) in the gender dysphoric groups 78.0 ± 8.9 than in the personality disorder cohort (53.0 ± 9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67 ± 0.57 and 0.56 ± 0.45 . Although they were nominally higher than the healthy normative controls (males: 0.32 ± 0.36 and females 0.41 ± 0.43), they were well within the non-pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

I. Partially prospective, non-blinded, observational studies with cross-sectional designs that had no control groups

Leinung et al. conducted a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p < 0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to-male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (> 32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (> 32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients. Of participants 36.4% were employed in jobs requiring a high school degree or less; 28.1% (excluding students) were on disability and/or unemployed. Rates of disability and unemployment were higher in male-to-female patients (31.8%) than female-to-male patients (14.0%). Mental health diagnoses reportedly were the major reason for disability. HIV infection and substance abuse were higher in male-to-female patients than female-to-male patients (8.3% versus 0% and 12.5% versus 6.0% respectively).

m. Retrospective, non-blinded, observational, longitudinal studies

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design of population treated with hormones, as well as, reassignment surgery and a population-based cohort. The investigators assessed mortality in patients who (a) were from a single-center, unspecified, university specialty clinic, (b) initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed by the clinic for at least 1 year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population was obtained through by the Central Bureau of Statistics of the Netherlands. Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio 1:2.4; $p < 0.0001$). The mean age at the time of hormone initiation in female-to-male and male-to-female patients was young: 26.1 ± 7.6 (range 16–56) years and 31.4 ± 11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p < 0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8 ± 6.3 and 19.4 ± 7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy as well as reassignment surgery. Of the patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI] 1.47-1.55) for males-to-females when compared to females in the general Dutch population. The small increase in all-cause mortality (12%) for females-to-males when compared to males in the general Dutch population was not statistically significant; 95% CI 0.87-1.42.

The major known contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide ($n=17$, SMR 5.70 [95% CI 4.93-6.54]), AIDS ($n=16$, SMR 30.20 [95% CI 26.0-34.7]), and illicit drug use ($n=5$, SMR 13.20 [95% CI 9.70-17.6]). An additional major contributor was “unknown cause” ($n=21$, SMR 4.00 [95% CI 3.52-4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and 6 (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients in older patients ($n=18$, SMR 1.64 [95% CI 1.43-1.87], mean age [range]: 59.7 [42-79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28-7.63], $p=0.01$). There was a smaller, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Although overall mortality was not increased in the hormone-treated female-to-male patients, there were more deaths due to illicit drug use than expected (SMR 25 [6.00-32.5]).

n. Retrospective, non-blinded, observational, longitudinal studies using matched national data

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were not delineated, but included evaluation and treatment by one of 6 specialized teams, name change, a new national identity number, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided. There were 804 patients identified with gender identity disorder (or related disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3±8.7 (range 20–62) and 36.3± 10.1 (range 21–69) respectively. Immigrant status was two times higher in reassigned patients (n=70, 21.6%) than in either type of control (birth [natal] sex matched n=294 [9.1%] or reassigned gender matched n=264 [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients (n=151 [57.8%]) than in either type of control (birth sex matched n=1,725 [61.5%] or reassigned gender matched n=1804 [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients (n=58, 17.9%) than in either type of control (birth sex matched n=123 [3.8%] or reassigned gender matched n=114 [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery (n=27 [8.3%]) than in controls (hazard ratio 2.8 [1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. The major contributor to this mortality difference was completed suicide (n=10 [3.1%]; adjusted hazard ratio 19.1 [5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients (n=9 [2.8%]) than in controls (hazard ratio 2.5 [1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery (n= 29 [9.0%] than in controls (adjusted hazard ratio 4.9 [2.9–8.5]). Male- to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons n= 64 [20.0%] than in controls (hazard ratio 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control. The increased risk for conviction of any crime or violent crime observed during the 1973-1988 interval was not seen later.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landen et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with “regret” in a national database. This same group (Landen et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra-group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least 1 year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After 2 years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures. (Dhejne et al., 2011) Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real-life experience phase, and family support.

Of the 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6]. The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.7% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. (This number [6.0%] appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense [usually in Thailand or the U.S.]. This cohort includes one person who was denied reassignment surgery by Sweden.)

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex-reassignment surgery outside of Sweden (36 of 41 after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male: male-to-female ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger than the entire female-to-male cohort (median age 22 versus 27 years) while the male-to-female applicants for reversal were older than the entire male-to-female cohort (median age 35 versus 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landen et al. extracted data from medical records and government verdicts. Logistic regression analyses were used identify relationships between variables. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different (albeit without Bonferroni correction) between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables has a more than additive effect.

The nationwide mortality studies by Dhejne et al. 2011 includes much, if not all, of the Landen (1998) patient population and most of the Dhejne (2014) population.

o. Randomized, non-blinded, longitudinal, some patients served as their own controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole et al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic. Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥ 2 year desire to change gender, a ≥ 1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at 6 months for diagnostic confirmation and exclusion of psychosis. Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity. The mean age and range of the entire cohort was 32.5 years (21-53).

Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms. Over the 2 year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic range for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior 2 years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct

statistical studies to compare the differences between the 2 cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities. Work status remained the same for post-operative patients which unemployment increased in the standard wait pre-operative cohort.

2. External Technology Assessments

- a.** CMS did not request an external technology assessment (TA) on this issue.
- b.** There were no AHRQ reviews on this topic.
- c.** There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.
- d.** There were two publications in the COCHRANE database, and both were tangentially related.

Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.

Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations
Boehmer U. *Am J Public Health*. 2002; 92: 1125-30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

f. There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. *NZHTA Report*. February 2002;1(1).
http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following: (1) Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists? And (2) If there is evidence of effectiveness, what subgroups would benefit from GRS?" Based upon the research, "Some 593 possibly relevant articles in abstract form were identified of which 70 articles were retrieved in full text."

The NZHTA stated, "The reviewed studies may indicate that early, rather than delayed, sex reassignment surgery is of greater benefit to transsexual people who have gone through rigorous assessment procedures and have been accepted for surgery. Also, the reviewed studies identify characteristics of groups defined as core and non-core transsexual people, but these characteristics are heterogeneous and anecdotal."

The NZHTA also stated, "Gender reassignment surgery may benefit some carefully assessed and selected transsexual people who have satisfied recognized diagnostic and eligibility criteria, and have received recognized standards of care for surgery. More research is required to improve the evidence base identifying the subgroups of transsexual people most likely to benefit from sex reassignment surgery."

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document:

Health Care for Transgender Individuals: Committee Opinion

Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gynecol. 2011;118:1454-8.

“Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient.”

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder
Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR,
Tompkins DA. *Arch Sex Behav.* 2012; 41:759–96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RCTs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. *J Clin Endocrinol Metab.* 2009;94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. www.wpath.org/files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf *Int J Transgend.* 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

The SOC were carefully reviewed because they are frequently cited as the basis of management by clinicians, including some of the clinical groups with whom CMS spoke used it as a flexible guide. In the WPATH's SOC Appendix D titled "Evidence for Clinical Outcomes of Therapeutic Approaches," WPATH noted, "One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective." They further reported, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria."

e. American Psychological Association

Suggested citation until formally published in the *American Psychologist*: American Psychological Association. (2015):

Guidelines for Psychological Practice with Transgender and Gender Nonconforming People

Adopted by the Council of Representatives, August 5 & 7, 2015.

www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and transaffirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. <http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx>

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LGBT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(I)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies took place in a or suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as "clients" instead of "patients," and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire (8) and how, in some instances, with hormone treatment for gender dysphoria, the depression lessens.

8. Public Comments

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups. All of the initial public comments are available at:

<https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n&bc=ACAAAAAAgAAAA%3d%3d&>

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage. Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.” *Heckler v. Ringer*, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section of the proposed decision provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

A. Analysis

1. Study Demographics

These studies were conducted in a total of 15 countries. Most were conducted in Europe (a total of 24 in Europe: Belgium four, Germany four, Holland two, Norway one, Spain two, Sweden four, Switzerland three, the United Kingdom three [not including the Barrett, 1998 study and the duplicative Megeri, Khoosal, 2007 study], and Yugoslavia one). One was in Asia (Singapore); one in South America (Brazil). Seven were conducted in North America (U.S. six, Canada one). One of the North American studies was a U.S.-conducted internet survey with non-U.S. and U.S. participants with a sub-analysis of the U.S. patients (Newfield et al., 2006).

All of the studies, with the exception of a national-wide mortality study (Dhejne et al., 2011), the international internet survey (Newfield et al., 2006), and the internet/convention site survey (Ainsworth, Spiegel, 2010), were conducted with patient populations from single sites. Many of these clinical centers cited in these studies were specialized tertiary referral centers offering comprehensive, integrated (psychiatric-psychological, endocrine, and surgical) care and whose staff could have been involved in both the patient care and the study. Of the studies reviewed, the Lawrence, 2006 study was conducted by a physician psychologist who surveyed the patient population of a single U.S. surgeon. The Ainsworth, Spiegel, 2010 study was conducted by a U.S. otolaryngologist with extensive surgery training who assessed the impact of facial feminization on transgender patients. The Hess et al. 2014 study was undertaken at a German university urologic specialty clinic. The Wolfradt, Neumann, 2001 study was conducted in Germany by a university otorhinolaryngologist and psychologist on patients who had undergone vocal cord surgery after reassignment surgery. The Rupp, Pfafflin 2015 study was undertaken by investigators who had seen the patients in a German forensic psychotherapy clinic.

2. Patient Population

Demographic assessments of the studies revealed that the mean ages of participants were in the 20s and 30s. (See Appendix C and Appendix D). Even when including standard deviation, most patients included in the study were under the age 60. Age of participants in the reviewed studies is important to assess generalizability to the Medicare population which is comprised predominantly of adults' age 65 years and older. While certain younger disabled adults are included in Medicare, generalizability of studies performed outside in the U.S. is likely reduced further since criteria to determine disability is unique to Medicare. When reporting ages of patients participating in studies, studies included mean age of population, but often failed to reveal standard deviation of the population. Most studies reported pre and post gender reassignment surgery ages, though some studies only reported post-surgery ages (Dehjne, 2011; Kuhn et al., 2009; Rakic et al., 1996; Rupp, Pfafflin, 2015; Udeze et al., 2008; Megeri, Khoosal, 2007; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993).

There was extensive lack of study participation and loss to follow-up in the published studies. (See Appendix C and Appendix G). This suggests that the population that seeks evaluation/treatment for gender dysphoria and/or applies for reassignment surgery is not the same population that undergoes reassignment surgery without hesitation or regret. The notable numbers of incomplete questionnaires similarly raises questions. This selection bias limits generalizability of any results.

3. Study Design

As noted earlier, a number of research designs were found when exploring the question, "Does gender reassignment surgery improve health outcomes for Medicare beneficiaries with gender dysphoria?" (See Appendix C). The vast majority of studies found were observational in nature though there was a single randomized trial (Mate-Kole et al., 1990) (see Figure 1). Two of the studies were blinded. (Hess, 2014; Lawrence, 2006) A total of 29 studies were not blinded. The blinding status of the two internet surveys is unknown (Ainsworth, Spiegel, 2010; Newfield et al., 2006).

Observational studies can be prospective, retrospective, or have components of both. But each observational study design has limitations, and may not be able to show the true association between gender/reassignment surgery and improved health outcomes. Limitations of observational studies include that they frequently generate unreliable findings, and they also generate bias; because of confounding, causal inferences cannot reliably be drawn. Thus these types of studies are limited in terms of evidentiary weight. Only a true experimental study (e.g., randomized clinical trial) has the potential to demonstrate a causal relationship between two factors.

In general, one of the advantages of prospective studies is that they could potentially help determine factors associated with improved outcomes due to their longitudinal observation over time, and the collection of results at regular time intervals minimizes recall error. However, retrospective studies have problems including: some key statistics cannot be measured, significant biases including selection bias, recall bias, and information bias may limit a retrospective study's applicability. Another problem with retrospective studies is that the temporal relationship between variables is frequently difficult to assess. Finally, it is difficult to control exposure or outcome assessment in a retrospective study design.

Studies that use controls as part of its research design have higher evidentiary weight than studies that lack controls. That is because the use of controls can help to eliminate the possibility of confounding. But controls by themselves are no guarantee of complete validity. In terms of the use of controls in these studies that we evaluated some studies had no concurrent controls; some studies used control groups, but they were not concurrent; some studies used semi-matched controls; and in other studies patients served as their own controls.

Seventeen observational studies, of which 10 used longitudinal and 7 used cross-sectional study designs, had formal control groups. In this group of studies, the cross-sectional studies used various controls including healthy volunteers and patients with other disorders or treatments. In this same group of studies, the longitudinal studies used various controls including the patients as their own serial control, other treatment groups in addition to having patients serve as their own controls, and control cohorts derived from national databases. Among the longitudinal studies with used patients as their own controls, 4 used self-report test instruments that were validated in large populations. Of these 4, 1 had more than 100 subjects, self-reported and others, or other cohorts using either national data or national registries. Some observational studies included in this analysis had surgery-only populations and used no controls, or used indirect controls incorporating normative testing. The remainder of the observational studies had mixed populations that included surgical patients and patients using other treatments or patients treated with non-genital gender reassignment surgical procedures. The studies that included groups with mixed populations either had no controls, or used indirect controls (statistical methods included ANOVA, correlation, or regression).

Our review included 25 prospective studies. Of these prospective studies, two used a retrospective approach to acquire data for a single parameter (Eldh et al., 1997; Johansson et al., 2009); one prospective study used a retrospective approach to acquire data for several parameters (Ruppin, Pfafflin, 2015); and one study used a

prospective approach beginning in 2005, but used a retrospective approach for data accumulated prior to that year (Leinung et al., 2013).

We found three retrospective studies (Asscheman et al., 2011; Dhejne et al., 2011; Landen et al., 1998). One study had at least a partially retrospective component, but with insufficient information to determine whether any of the data were obtained prospectively (Haraldsen, Dahl, 2000).

There were 11 longitudinal studies (Asscheman et al., 2011; Dhejne et al., 2011; Heylens et al., 2014; Kockott, Fahrner, 1987; Landen et al., 1998; Mate-Kole et al., 1979; Rakic et al., 1996; Rupp, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Ten of the longitudinal studies occurred in the group of studies with a designated control group (all of the above with the exception of Asscheman et al., 2011). In seven of the 11 longitudinal studies, the patients served as their own control over time before and after surgery (Heylens et al., 2014; Kockott, Fahrner, 1987; Meyer, Reter, 1979; Rakic et al., 1996; Rupp, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008).

There were 19 cross-sectional studies (Ainworth, 2010; Haraldsen, Dahl, 2000; Beatrice, 1985; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988; Wolfradt, Neumann, 2001; Blanchard et al., 1985; Weyers et al., 2009; Wierckx et al., 2011; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Salvador et al., 2012; Tsoi, 1993; Gómez-Gil et al., 2012; Hepp et al., 2005; Motmans et al., 2012; Newfield et al., 2006; Gómez-Gil et al., 2013; Johansson et al., 2009; Leinung et al., 2013). Of this number, two were cross-sectional with the exception of data collection for aspects of a single parameter that had occurred in the past (Eldh et al., 1997; Johansson et al., 2009), and one study asked participants to recall the status of a parameter prior to treatment (Wierckx et al., 2011a).

Seventeen of the studies had explicit control groups. Of the studies with explicit control groups, two studies derived controls from national databases (Dhejne et al., 2011 and 2014; Landen et al., 1998); five studies used the patients themselves as longitudinal controls (Heylens 2014a; Rakic et al. 1996; Rupp, Pfafflin, 2015; Smith et al., 2005a; Udeze et al., 2008; Megeri 2007); eight used various other controls (Ainsworth, Spiegel, 2010; Beatrice 1985; Haraldsen, Dahl, 2000; Kraemer et al., 2008; Kuhn et al., 2009; Mate-Kole et al., 1988 and 1990; Wolfradt, Neumann, 2001); and two studies used both treatment-type cohorts and patients themselves as controls (Kockott, Fahrner, 1987; Meyer, Reter 1979).

A number of studies consisted of surgical series, but in these studies there were no concurrent controls (Wierckx et al., 2011; Salvador et al., 2012; Blanchard et al., 1985; Tsoi, 1993; Eldh et al., 1997; Hess et al., 2014; Lawrence, 2006; Weyers, 2009a). In three surgical series normative data from psychometric instruments were used as the control (Blanchard et al., 1985a; Weyers 2009a; Wierckx et al., 2011b). In five surgical series, controls were lacking (except for the use of serial employment data in the Eldh et al. 1997 study) (Eldh et al., 1997; Hess 2014; Lawrence 2006; Salvador 2012; Tsoi, 1993).

Patients underwent a variety of surgical interventions in five studies. There were no controls. The role of surgical

intervention was assessed indirectly post-hoc by statistical techniques (analysis of variance and regression) (Gomez-Gil et al., 2012 and 2014; Hepp et al., 2005; Motmans et al., 2011; Newfield et al., 2006).

As mentioned in previous paragraphs, some prospective studies included in this analysis were cross-sectional in nature, and consisted of treated cohorts using a normative test, or a treatment cohort along with volunteer healthy cohorts. However, as we have noted, cross-sectional studies also have their limitations, including inability to determine temporal relationship between exposure and outcome (lacks time element). In other words, findings noted in a cross-sectional design cannot be inferred, because only current health and exposure to interventions are being studied. Also measurement error is an issue. Longitudinal studies with controls are most appropriate for determining this relationship between exposure and outcomes.

Observational studies have limitations. The lack of blinding has the potential to interfere with patient reported outcomes, which by their nature are subjective. Observational studies are prone to selection bias. Patients who seek treatment may not be the same as those who complete treatment-particularly if there are serial steps in the treatment process. (See Appendix G) Cross-sectional studies are prone to confounding. The impact of a particular step in a multi-faceted treatment process cannot be ascertained. The lack of a control group does not permit attribution of any outcome change to a specific intervention. There were seven studies where the patients themselves serve as longitudinal controls. The lack of a control makes it difficult to assess the results because there is not another group to make comparisons.

4. Psychometric Measurement Tools

There is also myriad use of measurement tools to assess patients suffering with gender dysphoria. (See Appendix E for a list of Psychometric Measurement tools.)

Some of the domains addressed in psychometric measurement tools measure the degree of depression and anxiety, body imagery, quality of life, identity traits, general wellbeing, physical and psychological function, self-concept, and others. Some of these measurement tools have been validated for patients with this condition, while others have been validated for other medical conditions. Some of the measurement tools found in this assessment were self-developed and there is no mention of validity when trying to determine if the test reliably measures what it is intended to measure.

5. Study Endpoints

A wide variety of study endpoints were used. Endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Some of the endpoints included

patient reported quality of life (QOL) as manifest by psychometric testing, sense of well-being, body imagery, anxiety and depression, sexual function and satisfaction, and social function. Objective endpoints included employment status, psychiatric function, and morbidity and mortality as well as adverse events.

Thirty of the studies employed 31 psychometric tools or investigator designed self-report surveys. (See Appendix E) Twenty investigators designed their own measurement tools or modified those of others.

External information on test validity, the size/composition of the reference population(s), diagnostic cut-points, and scoring was often not available because it was unpublished, proprietary, or in a non-English language. Six of the instruments, all non-specific, (the European QOL Survey, MMPI, SF-36, SCL-90, TSCS, and WHO-QOL-BREF), appear to have substantive normative data for comparative scoring (i.e., reference populations (≥ 1000) and obtained through representative sampling). Although these tools had been validated in a reference population, none had been validated in populations with gender dysphoria. Furthermore the investigators did not provide diagnostic cut-points and did not pre-specify the magnitude of test score change or test score difference considered to be biologically significant so the clinical importance could not be easily ascertained.

Only four investigator groups used only these psychometric tools validated in other large populations as their test instrument (Beatrice, 1985; Haraldsen, Dahl, 2000; Motmans et al., 2012; Newfield et al., 2006). Nine investigator groups used a mix of psychometric tools validated in large normative populations, less well validated tools, and/or self-designed tools (Ainsworth, Spiegel, 2010; Blanchard et al., 1985a; Gomez-Gil et al., 2014; Heylens 2014a; Ruppin, Pfafflin, 2015; Smith et al., 2005a (Udeze et al., 2008; Megeri 2007; Weyers 2009a; Wierckx et al., 2011b). Nine investigators used self-designed tools as their only test instrument (Eldh et al., 1997; Hess 2014; Johansson et al., 2009; Kockott, Fahrner, 1987; Lawrence, 2006; Meyer, Reter 1979; Rakic 1996; Salvador 2012; Tsoi 1993). A single investigator did not use any type of testing tool and provided only descriptive statistics (Leinung et al., 2013).

Three studies reported on complications linked or possibly linked to hormone treatment (Asscheman et al., 2011; Dhejne et al., 2011; Leinung et al., 2013), six studies reported on complications from reassignment surgery (Eldh et al., 1997; Lawrence, 2006; Ruppin, Pfafflin, 2015; Smith et al., 2005; Weyers et al., 2009; Wierckx et al., 2011). One study reported on serious and formalized regret for undergoing reassignment surgery (Landen et al., 1998), and one study reported on a patient with suicidal ideation who requested phallus removal (Meyer, Reter, 1979). Others reported on less severe or less formalized levels of regret. Five studies reported on the treatment or diagnosis of psychiatric disease (Dhejne et al., 2011; Haraldsen, Dahl, 2000; Hepp et al., 2005; Landen et al., 1998; Leinung et al., 2013; Meyer, Reter, 1979; Ruppin, Pfafflin, 2015; Udeze et al., 2008). Two studies reported on the history of psychiatric disease in their patient populations (Matte-Kole, 1988; Matte Kole, 1990).

Four studies reported on suicide attempts (Dhejne et al., 2011; Eldh et al., 1997; Heylens et al., 2013; Kockott, Fahrner, 1987), two studies reported on the history of suicide attempts in their patient population (Matte-Kole, 1988; Matte Kole, 1990). Three studies reported on suicide, of which one of them occurred incidentally (Asscheman et al., 2011; Blanchard et al., 1985; Dhejne et al., 2011). Two studies also reported on mortality (Asscheman et al., 2011; Dhejne et al., 2011).

There was a great degree of inconsistency in endpoints. Also endpoints were collected from a number of sources, including self-reporting, clinician assessment, and medical records as well national databases. Endpoints lacked operational definitions thus making their applicability difficult. CMS is interested in knowing what patients diagnosed with gender dysphoria believe are important endpoints that should be studied.

Mortality and Regret as Endpoints

Certain kinds of objective outcomes can be assessed by other types of study designs-albeit somewhat less robust. These include mortality and regret (as manifest by request for surgical reversal) when the data are rigorously prospectively collected in a comprehensive registry for all patients who have met specified entry criteria and treatment criteria.

More specifically, Swedish investigators extracted data from registries at the National Board of Health and Welfare to which all patients seeking reassignment surgery or reversal of reassignment surgery must make formal application. In the initial 1998 study, of the 233 applicants for reassignment surgery between July 1972 and June 1992, 20 were denied surgery, and subsequently 13 (3.8%) surgical patients requested return to the natal sex (Landen et al., 1998). In the 2014 follow-up study, of the 767 applicants for reassignment surgery or a change in legal status after surgery between 1960-2010, 86 were denied, and subsequently 15 (2.2%) requested reversal to the natal gender (Dhejne et al., 2014). Although the data from the two studies are not directly comparable because of the much shorter follow-up period in the latter study and although the analyses also did not consider other possible expressions of regret including suicide, the studies suggest that the majority of highly vetted patients in a structured care system do not express regret as defined by a formal request for return to natal gender status (Dhejne et al., 2011). The study, however, cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions.

Swedish investigators also conducted the most comprehensive study with functional endpoints of the 33 studies reviewed. This study relied on compulsory national databases (Dhejne et al., 2011) tracked all patients who had undergone reassignment surgery (at a mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls from the general population. They identified both increased mortality and increased psychiatric hospitalization. The mortality was primarily due to completed suicides (19.1-fold greater), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in control Swedes even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the sex of the control. For the same reasons as delineated above, this study cannot assess the impact of gender reassignment surgery per se because of the confounding introduced by the other interventions. The finding of this study demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant even in highly vetted patients in a structured care system.

B. Discussion

The question addressed in this NCD is whether there is sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria.

Gender dysphoria by the latest and prior nomenclature is a state in which there is incongruence between the gender assigned at birth and the gender(s) with which the person identifies. This incongruence may result in varying degrees of discontent and distress. Satisfaction and quality-of-life are well recognized as "latent variables" (hypothetical constructs) which cannot be measured directly (Borsboom et al., 2003; Newsom, 2015). As such, observable entities are used to infer or approximate satisfaction and/or quality-of-life. It may be challenging to identify parameters that truly reflect the nature and the magnitude of dysphoria in the individual. This challenge is followed by the need to know to what extent a specific test measures that which it purports to measure (test validity) and whether repeat testing will yield a comparable answer (test reliability).

The investigators of the clinical research reviewed in this NCD have attempted to measure dysphoria levels by objective data elements and by use of various psychometric and function scales/surveys. The objective data elements include a number of variables such as employment, morbidity, and formal requests for surgical reversal.

The psychometric tools used to assess outcomes have limitations. Many of the instruments that are most specific for the condition were designed by the investigators themselves or by other investigators in the field. In addition, the relevant diagnostic cut-points for scores and changes in scores that are clinically significant should be delineated to permit adequate interpretation of test results. As such, these studies were not definitive in nature.

Other factors might impact the utility of a given test. Patients undergo serial evaluations and a sequence of treatments (Bockting et al., 2011). These other interventions may reduce internal validity of the test. The affirmation and support obtained in psychotherapy-psychiatric care, the adjustment confidence gained in real life cross-gender behavior, and/or the physical and mental changes from hormone therapy may be (an) alternative cause(s) of the findings. Several studies suggest that there is a major therapeutic benefit from hormone therapy (Colizzi et al., 2013; Gómez-Gil et al., 2011; Gorin-Lazard et al., 2011, 2013; Heylens et al., 2014; Dubois, 2012). Another suggests that there is therapeutic benefit from time in the preferred gender role without other intervention (Greenberg, Laurence, 1981). As such, results from cross-sectional studies may be misleading. None of the studies used adequately matched controls over time. We believe longitudinal studies with serial assessment of the same patients would provide more robust answers. We note that even from the results from the four studies in which patients served as their own controls and which used an instrument known to be validated in large populations were negative (i.e., there was no improvement in psychometric or quality of life outcomes when patients were tested just prior to and at some point after the reassignment surgical intervention). (Heylens, 2014; Ruppín, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008). Further, rigorous studies with the use of appropriate comparison patients could better clarify the specific benefits and harms of each of the interventions.

CMS reviewed and considered potential objective measures of function including mortality, psychiatric treatment, and attempted suicide. None of the longitudinal studies in which patients served as their own control, however, comprehensively tracked changes in these events as objective measures of function before and after surgery. Events such as suicide and institutionalization were mentioned incidentally when describing patients excluded from a follow-up study or during the study (Heylens et al., 2014; Ruppín, Pfafflin, 2015). Other times investigators tracked these functional outcomes (e.g., psychiatric out-patient treatment, psychiatric in-patient treatment, and substance abuse) for the most current prior year (Ruppín, Pfafflin, 2015).

The most comprehensive study with functional endpoints, the Swedish study that followed all patients who had undergone reassignment surgery (at mean age 35.1 years) over a 30 year interval and compared them to 6480 matched controls, identified increased mortality and increased psychiatric hospitalization (Dhejne et al., 2011). The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. The divergence in mortality from the Swedish population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Unfortunately, the study was not constructed to assess the impact of gender reassignment *per se*. The finding of this study, again, demonstrated that reassignment surgery does not return patients to a normal level of morbidity risk and that the morbidity risk is significant, because of its clinical importance, its persistence over the interval of data collection and the increase in risk over time for the individual.

1. Patient Care

Additional questions regarding the care of patients with gender dysphoria remain. The specific type(s) of gender/sex reassignment surgery (genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific surgical procedures under study. Furthermore, most studies did not assess specific surgical procedures except for technical aspects. Surgical techniques have changed significantly over the last 60 years (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations presented a general framework and guidance on the care of transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH noted: "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care acknowledged the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

The surgical expertise and care setting(s) required to improve health outcomes in adults with gender dysphoria remain(s) uncertain. The selection of a particular surgeon could become an important variable if subjective outcomes depend on functional surgical results (Ross 1989). Many of these procedures involve complicated gynecologic, urologic surgical techniques accompanied by significant risk (Goddard et al., 2007a; Kuhn et al., 2011; Lawrence, 2003; Leclerc et al., 2015; Rachlin, 1999; Rupp, Pfafflin, 2015). Most of the studies for reassignment surgery have been conducted in northern Europe at select centers with integrated care (psychological, psychiatric, endocrinologic, and surgical) in which there is sequential evaluation of patients for progressively more invasive interventions.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care was often the centers' main focus rather than

2. Generalizability

With the variability in the study participants, providers and settings, the generalizability of the studies reviewed to the Medicare population is unclear. Many of the studies are old since they were conducted more than 10 years ago. Many of the programs were single-site centers without replication elsewhere. Most of these studies were conducted outside of the U.S. with far different medical systems for treatment and follow-up. The study populations were young and without significant physical or psychiatric co-morbidity. As noted above psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landen et al., 1998).

For the above reasons, it is difficult to generalize these studies to the Medicare population.

3. Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. There are, however, many gaps in the evidentiary base. These gaps have been delineated because they represent areas in which patient care can be optimized and which are opportunities for much needed research.

The Institute of Medicine, the National Institutes of Health, and others have delineated many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps.

The currently available evidence has limitations:

- There were design deficiencies. All but one of the studies were observational in nature. All but two were non-blinded. The accompanying loss to follow-up suggests that there is selection bias and that the population that seeks treatment for gender dysphoria is not the same population that undergoes reassignment surgery without hesitation or regret.
- The psychometric and psychosocial function endpoints are not well validated.

- There were limitations of the psychosocial endpoints and of the data collection of other hard functional outcomes. Evidence on mortality and especially suicide was stronger. The mortality and psychiatric hospitalization rates even after vetting in highly structured programs are of concern.
- There are insufficient data to select optimal candidates for surgery.
- The results were inconsistent, but negative in the best studies, i.e., those that reduced confounding by testing patients prior to and after surgery and which used psychometric tests with some established validation in other large populations. (Atkins et al., 2004; Balshem et al., 2011; Chan, Altman, 2005; Deeks et al., 2003; Guyatt et al., 2008a-c; 2011a-e; Kunz, Oxman, 1998; Kunz et al., 2007 and 2011; Odgaard-Jensen et al., 2011).
- Data on reassignment surgery performed on geriatric patients or follow-up data in geriatric patients who had reassignment surgery in the distant past is anecdotal (Orel, 2014).

C. Health Disparities

Four studies included information on racial or ethnic background. The participants in the 3 U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

D. Summary

Based on a thorough review of the clinical evidence available at this time, there is not enough evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria. There were conflicting (inconsistent) study results – of the best designed studies, some reported benefits while others reported harms. The quality and strength of evidence were low due to the mostly observational study designs with no comparison groups, potential confounding and small sample sizes. Many studies that reported positive outcomes were exploratory type studies (case-series and case-control) with no confirmatory follow-up. Due in part to the generally younger and healthier study participants, the generalizability of the studies to the Medicare population is also unclear. Additional research is needed. This proposed conclusion is consistent with the West Midlands Health Technology Assessment Collaboration (2009) that reported “[f]urther research is needed but must use more sophisticated designs with comparison groups.” WPATH also noted the need for further research: “More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.” Further, as mentioned earlier, patient preference is an important aspect of any treatment. With that in mind, CMS is interested in knowing from the patients with gender dysphoria what is important to them as a result of a successful gender reassignment surgery.

Knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. The specific role for various surgical procedures is less well understood than the role of hormonal intervention. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines and operating under European medical management and regulatory structures. Standard psychometric tools need to be developed and tested in the patients with gender dysphoria to validly assess long term outcomes. As such, further evidence in this area would contribute to the question of whether gender reassignment surgery improves health outcomes in adults with gender dysphoria.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Proposed Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on an individual claim basis. The Centers for Medicare & Medicaid Services (CMS) proposes to continue this practice and not issue a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria. Our review of the clinical evidence for gender reassignment surgery was inconclusive for the Medicare population at large. The low number of clinical studies specifically about Medicare beneficiaries' health outcomes for gender reassignment surgery and small sample sizes inhibited our ability to create clinical appropriateness criteria for cohorts of Medicare beneficiaries.

In the absence of a NCD, initial coverage determinations under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements will be made by the local Medicare Administrative Contractors (MACs) on an individual claim basis.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform the answer to the question posed in this proposed decision memorandum. Based on the gaps identified in the clinical evidence, these studies should focus on which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

We are requesting public comments on this proposed decision memorandum pursuant to section 1862(l)(3)(a) of the Act. We are specifically interested in public comments on the evidence we cited in this decision, comments containing any new evidence that has not been considered, and comments on whether a study could be developed that would support coverage with evidence development (CED), which would only cover gender reassignment surgery for beneficiaries who choose to participate in a clinical study.

X. Appendices

A. Appendix A

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 <i>Chapter: Psychosexual Disorders</i>	Trans-sexualism 302.5x [Gender Identity Disorder of Child-hood (302.6)]	Required A (cross- gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85
DSM III- Revised 1987 <i>TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence</i>	Trans-sexualism (TS) (302.50) [GID of C]	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1 ^o and 2 ^o sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans- sexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood , non- trans-sexual type, added			
DSM IV 1994 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex

DSM Version	Condition Name	Criteria	Criteria	Comments
			•e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex •Clinically significant distress or impairment in social, occupational, or other important areas of functioning	
DSM IV-Revised 2000 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder (Term transsexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 <i>Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders</i>	Gender Dysphoria (302.85)	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	•Marked discordance between natal 1° and 2° sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1° and 2° sex characteristics** •Marked desire to acquire 1° and 2° sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

DSM Version	Condition Name	Criteria	Criteria	Comments
			* or in young adolescents, the anticipated 2° sex characteristics ** or in young adolescents, prevent the development of the anticipated 2° sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: • Strong desire to be of the other gender or an insistence that one is of another gender. • Strong preference for cross-gender roles in make-believe play. • Strong preference for the toys, games, or activities of the other gender. • Strong preference for playmates of the other gender. • In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing • In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1°=primary
2°=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
 Non-randomized controlled trials
 Prospective cohort studies
 Retrospective case control studies
 Cross-sectional studies
 Surveillance studies (e.g., using registries or surveys)
 Consecutive case series
 Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	480 w GID who did not apply or were not approved for SRS were excluded	324	324 (100%)	-
Dhejne 2014 Landen	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 52 excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, & 16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1 & 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional		40	10 (25%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	Controlled	14 excluded for demographic matching reasons			The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender identity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional		119	119 (100%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.			Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results ¹⁰³ .
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S. respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal		1331	1177 (88.4%)	-

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No analysis by tx status	The number in the available patient pool was not specified.			
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference

B/C=because

BSRI=Bem Sex Role Inventory

F=Female

FP-R=Freiberg Personality Inventory

GD=Gender dysphoria

GID=Gender identity disorder

HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems

M=Male

NA=Not applicable

SCL-90=Symptom Checklist-90

SF-36=Short Form 36

GRS=Sex reassignment surgery

Tx=Treatment

W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery: 50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian

Author	Age (years, mean, S.D., range)	Gender	Race
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3±8.7 (20-62), M to F 36.3±10.1(21-69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landen	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7±4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M to F; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).		-

Author	Age (years, mean, S.D., range)	Gender	Caucasian
		W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio 1:1.6.	
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F to M: 27.8 (18–46), M to F 37.3 (21–60). Time of GRS: F to M: 31.4 (22–49), M to F 38.2 (22–57). Time of follow-up for post-GRS: F to M: 38.9 (28–53), M to F 46.0 (25–69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve <i>Smilkstein</i>	Published in 1978 Initial data: 152 families in the U.S. A “friends” component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory <i>Beck, Ward, Mendelson, Mock, & Erbaugh</i>	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. It is copyrighted and requires a fee for use
Bem Sex Role Inventory <i>Bem</i>	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire <i>Clement & Lowe</i>	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale <i>Lindgren & Pauly</i> <i>(Kuiper, Dutch adaptation 1991)</i>	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire)	Developed circa 1966 Manual published 1970

Instrument Name and Developer	Development and Validation Information
<i>Crown & Crisp</i>	Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey <i>Anderson, Mikulić, Vermeylen, Lyly-Yrjanainen, & Zigante,</i>	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index <i>Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen</i>	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Körpers <i>Strauss</i>	Published 1996 (German)
Freiberg Personality Inventory <i>Fahrenberg, Hampel, & Selg</i>	7 th edition published 2001, 8 th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" <i>Smith, van Goozen, Kuiper, & Cohen-Kettenis</i>	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale <i>Altstotter-Gleich</i>	Published 1989 (German)
General Health Questionnaire <i>Goldberg & Blackwell (initial study)</i> <i>Goldberg & Williams (manual)</i>	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale <i>Zigmond & Snaith</i>	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1 st 50 compared to 2 nd 50.
Inventory of Interpersonal Problems <i>Horowitz</i>	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psychotherapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire <i>Kelleher, Cardozo, Khullar, & Salvatore</i>	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory <i>Hathaway & McKinley</i>	Published in 1941 Updated in 1989 with new, larger, more diverse sample.

Instrument Name and Developer	Development and Validation Information
<i>Butcher, Dahlstrom, Graham, & Tellegen</i>	MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphilia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences <i>Wolfradt</i>	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" <i>Cohen-Kettenis & van Goozen</i>	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale <i>Rosenberg</i>	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 <i>RAND</i> <i>Ware & Sherbourne 1992</i> <i>McHorney, Ware, & Raczek 1993</i>	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale <i>Watson & Friend</i>	Initial publication in 1969 Requires permission for use
Social Support Scale <i>Van Tilburg 1988</i>	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire <i>Spielberger, Gorsuch, Lushene, Vagg, & Jacobs</i>	Current format published in 1983 Proprietary test
Symptom Checklist-90 <i>Derogatis, Lipman, Covi</i> <i>Derogatis & Cleary</i>	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale <i>Fitts & Warren</i>	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other information available. Requires qualification for use
Utrecht Gender Dysphoria Scale <i>Cohen-Kettenis & van Goozen</i>	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)

Instrument Name and Developer	Development and Validation Information
WHO-Quality of Life (abbreviated version) <i>Harper for WHO group</i>	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Criminality, Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landen	Yes	-	-	-	Includes demographics*	Criminality, Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS, STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscherman et al.	Yes	-	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2 nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Körpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 ($\pm$ R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.**Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets**

Author	Test	Patient and Data Loss	Results
Psychometric Test			
Heylens et al. Belgium 2014	SCL-90R	90 applicants for SRS were recruited. •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx. •12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical comorbidity, personal decision for no tx, or personal decision for only hormone tx. •1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. •1 (12.2% of initial recruits) had not yet received SRS by study close. 46 (51.1% of recruited) underwent serial evaluation •The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) missing data for another 1.1% to 11.1%.	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.
Ruppin,Pfafflin, Germany 2015	SCL-90R	The number in the available patient pool was not specified.	

Author	Test	Patient and Data Loss	Results
		140 received recruitment letters. •2 (1.4% of those with recruitment letters) had died. •1 (0.7%) was institutionalized. •5 (3.6%) were ill. •8 (5.7%) did not have time. •8 (5.7%) stated that GD was no longer an issue. •8 (5.7%) provided no reason. •28 (20.0%) declined further contact. •9 (6.4%) were lost to follow-up. 71 (50.7%) agreed to participate. •2 (1.4%) had not undergone SRS •The test was not completed by 9. missing data for another 6.4%.	At t=0, the "global severity index "SCL-90R score was 0.53 ± 0.49. At post-SRS follow-up the score had decreased to 0.28 ± 0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70 ± 0.67 at t=0 and 0.26 ± 0.34 post-SRS.
Smith et al. Holland 2005	MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. •103 (31.7%) were not eligible to start hormone tx & real-life experience. •34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. •36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0 ± 40.7. At post SRS-follow-up, the score had decreased to 120.3 ± 31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. •Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.

Author	Test	Patient and Data Loss	Results
			There were no statistically significant changes in the global score or for any of the subscales.
National Databases			
Dehjne Sweden 2011	Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. •480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. •All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9-8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0-3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landen et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. •All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID=NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery
Tx=Treatment [Back to Top](#)

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID: 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstötter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentität* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid-Technique as shown at the example of the assessment of gender identity], Verlag für empirische Pädagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients.* 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to-male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry.* 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel-Journel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 June;328(19):1490-4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA*. 2010 Summer-Fall;22(4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristoni J, Menggiola MC, Jannini EA, Manfell C, Corona G, Morandi M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res*. 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013 Mar;13(3):214-22. Epub 2012 Dec 21. PMID: 23260128.

Barlow DH, Abel GG, Blanchard EB. Gender identity change in transsexuals. Follow-up and replications. *Arch Gen Psychiatry*. 1979 Aug;36(9):1001-7. PMID: 464738.

Barrett J. (1998) *Psychological and social function before and after phalloplasty*. University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or *IJT*. 1998; 2:1 or <http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal.pdf>.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav*. 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav*. 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med*. 2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis*. 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism. *Fertil Steril*. 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril*. 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology*. 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg*. 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol*. 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheeran B, Smith L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav*. 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes*. 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, management* (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav*. 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry*. 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med*. 2011 Jun 30;364(26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow-up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25(3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health.* 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am.* 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med.* 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev*. 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics*. 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav*. 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)*. 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav*. 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth*. 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self-injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med*. 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol*. 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex*. 2006;51(3):53-69. PMID: 17135115.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res*. 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT. Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend*. 2011;13:165–232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from a household probability sample of adults. *Am J Public Health*. 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol*. 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women’s souls: Personal narrative of Thailand’s transgendered youth*. Routledge.

Costantino A, Cerpolini S, Alvisi S, Morselli P, Venturoli S, Meriggiola M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther*. 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148-53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry*. 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry*. 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril*. 2010 Dec;94(7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav*. 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Elaut E, Heylens G, van Maele G, Selvaggi G, T'Sjoen G, Rubens R, Hoebeke R, Monstrey S. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *J Sexol*. 2006;15:126-33. (Not in PubMed)

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry*. 2007 Apr;22(3):137-41. Epub 2006 Dec 26. PMID: 17188846.

Trial Collaborative Group, European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess*. 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male-to-female transsexual after initiation of hormone therapy. *J Clin Neurosci*. 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull*. 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry*. 1974;7(0):79-110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol*. 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis*. 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gyneco*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186(2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Langstrom N, Landén M. Long term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6(2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav*. 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol*. 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduyn T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*. 2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav*. 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol*. 2011 Jun;51(2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis*. 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan-Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub*. 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinić B, Barišić J, Djordjevic ML, Vujović S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal*. 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72(1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg*. 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20(6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikulić B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview*. EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrz M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work*. EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Fares WH. The 'availability' bias: underappreciated but with major potential implications. *Crit Care*. 2014 Mar 12;18(2):118. PMID: 25029621.

Ferring D, Filipp SH. Messung des Selbstwertgefühls: Befunde zu Reliabilität, Validität und Stabilität der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica*. 1996; 42: 284-292. German. (Not in PubMed)

Ferron P, Young S, Boulianne C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med*. 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry*. 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab*. 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexual surgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir*. 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res*. 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav*. 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl*. 2011 May;13(3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol*. 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev*. 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol*. 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril*. 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand*. 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165(4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNiel D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law*. 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int*. 2007 Sep;100(3):607-13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website:
<http://www.stat.berkeley.edu/users/hhuang/141C-2008.html>. Section Website:
<http://www.stat.berkeley.edu/users/mgoldman>.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess*. 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav*. 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav*. 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav*. 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero-Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012 May;37(5):662-70. Epub 2011 Sep 19. PMID: 21937168.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res*. 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res*. 2005;64 Suppl 2:31-6. PMID: 16286768.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia*. 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes*. 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross-sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol*. 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med*. 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia*. 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012 Feb;9(2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis*. 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict*. 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res*. 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol*. 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis*. 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment*. 1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonasate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav*. 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 3;336(7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652): 1049-51. Erratum in: *BMJ*. 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol*. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol*. 2011 Dec;64(12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex*. 2011;58(1):10-51. PMID: 21213174.

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery*. 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007 Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand*. 2000 Oct;102(4):276-81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13(4):364-8. PMID: 13463138.

Hathaway SR, Reynolds PC, Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt*. 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res*. 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry*. 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics/objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services. Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology*. 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel)*. 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand*. 1971;47(1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel)*. 1973;6(2):65-80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat*. 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21;(1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol*. 1988 Dec;56(6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci*. 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav*. 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav*. 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile in transsexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B-Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha-reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013.
<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. <http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf>.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex*. 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol*. 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS*. 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltan R, Kawachi I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med.* 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav.* 2010 Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal.* 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab.* 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co-morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hiort O, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav.* 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci.* 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics.* 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav*. 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child*. 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav*. 1987 Dec;16(6):511-22. PMID: 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav*. 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences*. Stanford, Calif.: Stanford University Press, 1966.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. *Psychopathology*. 2008;41(2):96-100. Epub 2007 Nov 23. PMID: 18033979.

Krege S, Bex A, Lümnen G, Rübber H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollver H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol*. 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hildebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol*. 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6. PMID: 18990387.

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5. DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician*. 2013 Oct 15;88(8):Online. PMID: 24364581.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res*. 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation*. 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet*. 2011 April 9;377: 1211. PMID:2 1481690.

Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand*. 1998 Apr;97(4):284-9. PMID: 9570489.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol*. 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav*. 1999 Dec;28(6):581-3. PMID: 10650442.

Lawrence A. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003 Aug;32(4):299-315. PMID: 12856892.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav.* 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav.* 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Arch Sex Behav.* 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract.* 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lief HI, Hubschman L. Orgasm in the postoperative transsexual. *Arch Sex Behav*. 1993 Apr;22(2):145-55. PMID: 8476334.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav*. 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand*. 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975 Nov;4(6):639-56. PMID: 1212093.

Lioudaki E, Ganotakis ES, Mikhailidis DP, Nair DR. The estrogenic burden on vascular risk in male-to-female transsexuals. *Curr Pharm Des*. 2010;16(34):3815-22. PMID: 21128891

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav*. 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav*. 1979 Sep;8(5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav*. 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess*. 1984 Oct;48(5):500-7. PMID: 6389823.

Lundström B, Pauly I, Wålinder J. Outcome of sex reassignment surgery. *Acta Psychiatr Scand*. 1984 Oct;70(4):289-94. PMID: 6388248.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev*. 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D, Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grütters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab*. 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Mataix-Cols D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav*. 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry*. 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry*. 1990 Aug;157:261-4. PMID: 2224377.

Maycock L, Kennedy H. Breast care in the transgender individual. *J Midwifery Womens Health*. 2014 Jan-Feb;59(1):74-81. Epub 2013 Nov 13. PMID: 24224502.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med*. 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database*. 2009. No.3. www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2009/LGBTHealth030409finalversion.pdf.

Medraś M, Józków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol*. 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy*. 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health*. 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self-prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med*. 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl*. 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):607-15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

D- Meyer JK. Clinical variants among applicants for sex reassignment. *Arch Sex Behav*. 1974 Nov;3(6):527-58. PMID: 4429437.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10(4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav*. 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Ansseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miles C, Green R, Hines M. Estrogen treatment effects on cognition, memory and mood in male-to-female transsexuals. *Horm Behav*. 2006 Dec;50(5):708-17. Epub 2006 Aug 1. PMID: 16884726.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics*. 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient-subjects. *J Med Ethics*. 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol*. 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg*. 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. Spanish.

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med*. 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav*. 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollner H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med*. 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care*. 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015*. (Portland State quantitative methods) www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med*. 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. *J Acquir Immune Defic Syndr*. 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health*. 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health*. 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

Odgaard-Jensen J, Vist GE, Tinnner A, Kunz R, Alt EA, Schunemann H, Briel M, Nordmann A, Pugno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2011 Apr 13;(4):MR000012. PMID: 21491415.

O'Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J*. 1981;50(1):46-9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res*. 2008 Jan 15;157(1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med*. 2011 Feb;165(2):171-6. PMID: 21300658.

Olsson SE, Jansson I, Moller A. Men as women. Experiences from five case after administrative, hormonal, and surgical treatment. *Nord J Psychiatry*. 1996;50(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav*. 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long-term follow-up. *Arch Sex Behav*. 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr*. 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav*. 2011 Apr;15(3):674-82. PMID: 21604064.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex*. 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögenderfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to-male transsexuals. *J Sex Med*. 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res*. 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to-female transsexual persons. *J Voice*. 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology*. 2005 Jul;16(4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968 Nov;147(5):460-71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15(1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril*. 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med*. 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work*. 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues of utility and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 May 23;7:9. PMID: 22621419.

Phillips J, Frances A, Cerullo MA, Charuvaodyne J, Decker HS, First MB, Chae M, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a plurilogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims*. December 2009. <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf>.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To-Male Genital Reconstructive Surgery. *IJT*. 1999 Jul-Sept;3(3). (Not in PubMed) <http://www.symposion.com/ijt/ijt990302.htm>
<http://www.iiav.nl/eazines/web/ijt/97-03/numbers/symposion/ijt990302.htm>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res*. 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res*. 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J*. 1959 Dec 26; 2(5164): 1448-52. PMID: 14436154.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):*Trans-sexualism and Sex reassignment*. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res*. 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav*. 1999 Feb;28(1):71-89. PMID: 10097806.

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand*. 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav*. 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl*. 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav*. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health*. 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract*. 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18(88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193-236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carroll RA. New women: Sexological outcomes of male-to-female gender reassignment surgery. *JSET*. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg*. 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol*. 2011 May;8(5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol*. 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer*. 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law*. 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology*. 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT*. 2001 Jul-Sept; 5(3):20 pages.
http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev*. 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract*. 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract*. 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001
Printed on 7/25/2016. Page 133 of 145

Apr;40(4):472-81. PMID: 15842032.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res*. 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand*. 1981 May;63(5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand*. 1981 Jul;64(1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav*. 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

J Am Acad Child Adolesc Psychiatry. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):192-206 Epub 2010 Mar 29. PMID: 20347346.

Steinle K. Hormonal management of the female-to-male transgender patient. *Midwifery Women's Health*. 2011 May-Jun;56(3):293-302. PMID: 21535376.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav*. 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J*. 1972 Mar;68(3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat*. 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBek), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Stroumsa D. The state of transgender health care: policy, law, and medical frameworks. *Am J Public Health* . 2014 Mar;104(3):e31-8. Epub 2014 Jan 16. PMID: 24432926.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev*. 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills*. 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2004 Dec;19(6):301-12. PMID: 15724806.

Swaab DF, Garcia-Falgueras A. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Funct Neurol*. 2009 Jan-Mar;24(1):17-28. PMID: 19403051.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res*. 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res*. 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female-to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand*. 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman J. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry.* 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand.* 1988 Oct;78(4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J.* 1992 Apr;33(2):182-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J.* 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore.* 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess.* 1979. Aug;43(4):385-7. PMID: 383946.

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007 Oct;83(984):638-42. PMID: 17916872.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol*. 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol*. 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedeker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab*. 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsen I. T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierzak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med*. 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. *Arch Sex Behav*. 2015 Jul;44(5):1281-7. Epub 2015

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav*. 2013; 42:361-70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav*. 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med*. 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mirošević Marojević L, Nović M, Tandić Gajić M, Stojanović M, Marina L V, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal*. 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow- up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry*. 1978;132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Weigert R, Frison E, Sessieq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology*. 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quality of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people. Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV*. World Health Organization. July 2015. <http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/>.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*. 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van De Peer F, Dedeker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedeker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med*. 2012 Oct;9(10):2641-51. Epub 2012 Aug 20. PMID: 22906135.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

B-Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. *J Sex Med*. 2014 May;11(5):1240-7. Epub 2014 Mar 12. PMID: 24618412.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction*. 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health*. 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex*. 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S. The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract*. 1999; 49 (449): 991-2. PMID: 10824346.

Wilson RC, Nimkarn S, Dumic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic-specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. *Mol Genet Metab*. 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab*. 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect*. 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol*. 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav*. 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol*. 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav*. 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders*. (6th version) February, 2001.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr.* 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez-Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab.* 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals.* (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5 α -Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopoulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg.* 2006 May;77(5):432-8. German. Erratum in *Chirurg.* 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis.* 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry*. 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res*. 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901-14. PMID: 23868018.

[Back to Top](#)

EXHIBIT G

Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

[Back to Top](#)

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Final Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: August 30, 2016

I. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
 AIDS - Acquired Immune Deficiency Syndrome
 ANOVA - Analysis of Variance
 APA - American Psychiatric Association
 APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
 BIQ - Body Image Questionnaire
 BSRI - Bem Sex Role Inventory
 CCEI - Crown Craps Experimental Index
 CDC - Centers for Disease Control
 CHIS - California Health Interview Survey
 CI - Confidence Interval
 CMS - Centers for Medicare & Medicaid Services
 DAB - Departmental Appeals Board
 DSM - Diagnostic and Statistical Manual of Mental Disorders
 EMBASE - Excerpta Medica dataBASE
 FBeK - Fragebogen zur Beurteilung des eigenen Körpers
 FDA - Food and Drug Administration
 FPI-R - Freiburg Personality Inventory
 FSFI - Female Sexual Function Index
 GAF - Global Assessment of Functioning
 GID - Gender Identity Disorder
 GIS - Gender Identity Trait Scale
 GRS - Gender Reassignment Surgery
 GSI - Global Severity Indices
 HADS - Hospital Anxiety Depression Scale
 HHS - U.S. Department of Health and Human Services
 HIV - Human Immunodeficiency Virus
 IIP - Inventory of Interpersonal Problems
 IOM - Institute of Medicine
 KHQ - King's Health Questionnaire
 LGB - Lesbian, Gay, and Bisexual
 LGBT - Lesbian, Gay, Bisexual, and Transgender
 MAC - Medicare Administrative Contractor
 MMPI - Minnesota Multiphasic Personality Inventory
 NCA - National Coverage Analysis
 NCD - National Coverage Determination
 NICE - National Institute for Health Care Excellence
 NIH - National Institutes of Health
 NZHTA - New Zealand Health Technology Assessment
 PIT - Psychological Integration of Trans-sexuals
 QOL - Quality of Life
 S.D. - Standard Deviation
 SADS - Social Anxiety Depression Scale
 SCL-90R - Symptom Check List 90-Revised
 SDPE - Scale for Depersonalization Experiences
 SES - Self Esteem Scale

SF - Short Form

SMR - Standardized Mortality Ratio SOC - Standards of Care

STAI-X1 - Spielberger State and Trait Anxiety Questionnaire

STAI-X2 - Spielberger State and Trait Anxiety Questionnaire

TSCS - Tennessee Self-Concept Scale

U.S. - United States

VAS - Visual Analog Scale

WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100

WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Although there are other therapeutic options for gender dysphoria, consistent with the NCA request, this decision only focuses on gender reassignment surgery.

B. Prevalence of Transgender Individuals

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

Most recently, the Williams Institute published a report that utilized data from the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS). Overall, they found that 0.6% or 1.4 million U.S. adults identify as transgender. The report further estimated 0.7% of adults between the ages of 18-25 identify as transgender, 0.6% of adults between the ages of 25-65 identify as transgender, and 0.5% of adults age 65 or older identify as transgender (Flores et al., 2016).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. (CMS Office of Minority Health 2015).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson and Moller 2003).

III. History of Medicare Coverage

Date	Action
August 1, 1989	CMS published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.

CMS does not currently have a NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a NCA for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A) Under §1832 (Scope of Part B)
 Under §1861(s) (Definition of Medical and Other Health Services)
 Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
December 3, 2015	CMS accepts an external request to open a NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.
June 2, 2016	Proposed Decision Memorandum posted on the web site and the final 30 day public comment period commenced.
July 2, 2016	Final comment period closed. CMS received 45 comments.

V. FDA Status

Surgical procedures per se are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved and/or cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We also considered articles cited by the requestor, articles identified in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies for gender dysphoria. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) and/or quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), suicide (attempts), mortality, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). Reliability and validity are important because when evaluating patients with gender dysphoria most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded. The CMS initial internal search for the proposed decision memorandum was limited to articles published prior to March 21, 2016. The CMS internal search for the final decision memorandum continued through articles published prior to July 22, 2016.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early

termination, completed, ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. For this final decision, CMS also reviewed all evidence submitted via public comment.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this specific NCA, CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as one study (Udeze et al., 2008; Megeri and Khoosal, 2007). A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study. The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

Figure 1 Legend: The studies in Figure 1 are categorized into three groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only population box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of patients whose treatment could involve a variety of therapeutic interventions, but who were not stratified by that treatment.

When looking at the totality of studies, the 33 studies could be characterized by the following research design groups:

a. Observational, mixed population of surgical and non-surgical patients without stratification

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635-42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design to assess a mixed population treated with hormones, as well as, reassignment surgery in comparison to a population-based cohort. The study was not designed to assess the specific impact of gender reassignment surgery on clinical outcomes.

The investigators assessed mortality in patients who (a) were from a single-center, unspecified, Dutch university specialty clinic, (b) had initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed (with or without continued hormone treatment) by the clinic for at least one year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population were obtained through the Central Bureau of Statistics of the Netherlands (Centraal Bureau voor de Statistiek). Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio difference 1:2.4 with a p-value $p < 0.0001$). Later calculations did not distinguish between those with hormone therapy alone versus those with hormone therapy plus reassignment surgery. The mean age at the time of hormone initiation in female-to-male and male-to-female patients was 26.1 ± 7.6 (range 16–56) years and 31.4 ± 11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p < 0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8 ± 6.3 and 19.4 ± 7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy with or without surgical reassignment. Of these patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality for this mixed population was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI] 1.47–1.55) for males-to-females when compared to males in the general Dutch population. The increase in all-cause mortality (12%) for females-to-males when compared to females in the general Dutch population was not statistically significant (95% CI 0.87–1.42).

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients but only in older patients ($n=18$, SMR 1.64 [95% CI 1.43–1.87]), mean age [range]: 59.7 [42–79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28–7.63], $p=0.01$). There was a small, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Other contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide ($n=17$, SMR 5.70 [95% CI 4.93–6.54]), AIDS ($n=16$, SMR 30.20 [95% CI 26.0–34.7]), and illicit drug use ($n=5$, SMR 13.20 [95% CI 9.70–17.6]). An additional major contributor was “unknown cause” ($n=21$, SMR 4.00 [95% CI 3.52–4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and six (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Overall mortality, and specifically breast cancer and cardiovascular disease, were not increased in the hormone-treated female-to-male patients. Asscheman et al. reported an elevated SMR for illicit drug use ($n=1$, SMR 25

Printed on 11/17/2016. Page 11 of 150

This study subsumes earlier publications on mortality (Asscheman et al. 1989 [n=425]; Van Kesteren et al. 1997 [n=816]).

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone- treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1 ± 8.0 . HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87 ± 9.15 years (range 15-61). The current age of patients using hormones was 33.6 ± 9.1 years (n=120) and older than the age of patients without hormone treatment (25.9 ± 7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6 ± 8.1 years.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female (ratio 1:1.7). The number of patients not on hormones and who had undergone at least one gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, and/or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and/or vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was 9 in transsexuals without hormone treatment and 6.4 in transsexuals with hormone

treatment. The mean scores for HAD Anxiety, HAD Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery undergoing various stages of treatment.

The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center (Barcelona, Spain), specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but not genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty). The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL- BREF) was used to evaluate quality of life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

All consecutive patients presenting at the clinic (277) were recruited and, 260 (93.9%) agreed to participate. Of this number, 59 of these were excluded for incomplete questionnaires, 8 were excluded for prior genital reassignment surgery, and 193 were included in the study (the mean age of this group was 31.2 ± 9.9 years (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients (ratio 1:1.6). Of these, 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy $n=19$ (25.7%); mastectomy $n=29$ (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least one non-genital surgical procedure with mammoplasty augmentation being the most common procedure, $n=47$ (39.5%), followed by facial feminization, $n=11$ (9.2%), buttocks feminization, $n=9$ (7.6%), and vocal feminization (thyroid chondroplasty), $n=2$ (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81 ± 14.89 (range 12.50-96.88), "Physical" 63.51 ± 17.79 (range 14.29-100), "Psychological" 56.09 ± 16.27 (range 16.67- 56.09), "Social" 60.35 ± 21.88 (range 8.33-100), and "Global QOL and Health" 55.44 ± 27.18 (range 0-100 with higher score representing better QOL). The mean APGAR family score was 7.23 ± 2.86 (range 0-10 with a score of 7 or greater indicative of family functionality).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all four domains and

the general health and quality of life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a single-site (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2 ± 10.3 years. Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

HADS scores were missing for at least one person. The HADS test revealed non-pathologic results for depression (female-to-male: 6.64 ± 5.03 ; male-to-female: 6.58 ± 4.21) and borderline results for anxiety (female-to-male: 7.09 ± 5.11 ; male-to-female: 7.74 ± 6.13 , where a result of 7-10 = possible disorder). There were no differences by natal gender. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted a two center (Lund and Umeå, Sweden) non-blinded, observational study using a

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥ 1 year of real-life experience in preferred gender, and ≥ 1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment five or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) two or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a three or five point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified except for GAF, which pre-specified a difference to mean change ≥ 5 points. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, 42 (70.0% of eligible) (17 [40.5 %] female-to-male; 25 [59.5%] male-to-female; ratio 1:1.5) were available for follow-up. Of these, 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including one post mastectomy), five were still in the process of completing surgery, and five (one female-to-male; four male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The age (ranges) of the patients at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22- 49), and 38.9 (28-53) years in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) years in the male- to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p < 0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improved in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to- female patients. A ≥ 5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these 42 patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery ($n=32$) and mastectomy only ($n=one$), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38.1%) (41.2% of female- to-male; 36.0% of male-to-female patients) were reported to have a partner. Yet more than that number commented on partner relationships: (a) 62.2 % of the 37 who answered (50.0% of female- to- male; 69.6% of male-to-female patients) reported improved partner relationships (five [11.9%] declined to answer.); (b) 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female patients) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification. In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers.

This study subsumes earlier work by Bodlund et al. (1994, 1996). The nationwide mortality studies by Dhejne et al. (2011) may include all or part of this patient population.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a single-center (Albany, New York) a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p < 0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; Of the patient population, 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to- male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality of life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single Belgian university specialty clinic at Ghent. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 years (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metaoidplasty eight (with five of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation three.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality of life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metaoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality of life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al. or Weyers et al. is unknown.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed population with and without hormone therapy and/or reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the Short-Form 36 (SF-36) Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the eight domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males-or-females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6 ± 10.8 years. Of these 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. Of these, 254 (67.0%) reported prior or current testosterone use while 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery.

Complete SF-36 data were available for 376 U.S. respondents. For the complete, non-stratified U.S. cohort the Physical Summary Score (53.45 ± 9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was within one standard deviation of the normative mean. The Mental Summary Score (39.63 ± 12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was well within two standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12 ± 10.2), Role Emotional (42.42 ± 11.6), Social Functioning (43.14 ± 10.9), and Vitality (46.22 ± 9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within one standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22 ± 11.9) than those with "No Testosterone Usage" (36.08 ± 12.6) ($p=0.001$). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21 ± 11.6) and those without "Top Surgery" (38.01 ± 12.5) ($p=0.067$). These differences were well within one standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

b. Observational, surgical series, without concurrent controls

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun; 53(3):295-304.

Blanchard et al. conducted a single-center (Ontario, Canada), prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least one year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using Blanchard's Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R). Differences in test scores considered to be biologically significant were not pre-specified in the methods.

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 263 were diagnosed with gender dysphoria. Of these 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically ($p=0.01$).

Additional surgical procedures in female-to-male patients included: oophorectomy/hysterectomy (92.1%) and phalloplasty (7.9%). Additional surgical procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation (53.1%). Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis (100%) and breast implantation (33.3%). The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all three patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 65.2% of female-to-male patients cohabitated with partners of their natal gender; 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; and no male-to-female patients with female partner preference cohabitated with partners of their natal gender.

Of participants, 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (one female-to-male; one male-to-female with male partner preference; three male-to-female with female partner preference) indicated that they probably would undertake the surgery again. Post hoc analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with an investigator designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery.

Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; eight (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their sexual orientation; 13 (26%) declined to answer the question. The study found that two female-to- male patients and two male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

Hess et al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed anonymous questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic (Essen, Germany). Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44 ± 9 (range 18-70) years and mean duration after surgery was 3 ± 1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality of life was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed in the more distant past; whereas, more satisfaction with vaginal depth and width was present in more recent surgical treatment.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun; 66(4):371-2. PMID: 22624747.

Salvador et al. conducted a single center (Port Alegre, Brazil) prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 82 underwent sex reassignment surgery. There were 69 participants with a minimum 2-year follow up, of whom 52 patients agreed to participate in the study. The age at follow-up was 36.3 ± 8.9 (range 15-58) years with the time to follow-up being 3.8 ± 1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J*. 1993 Dec; 34(6):515-7.

Tsoi conducted a single-center (Singapore) prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigator assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥ 6 months, and willingness to function in the life of the desired gender for ≥ 6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 (44.4%) were female-to-male and 45 (55.6%) were male-to-female (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4 ± 4.4 (range 14-36) and 27.4 ± 4.0 ; (range 14-36); male-to-female 22.9 ± 4.6 (range 14-36) and 24.7 ± 4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender

reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p < 0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

Weyers et al. (2009) conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with two self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior four weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center (Ghent, Belgium), specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed seven question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 (71.5% of the eligible recruits) participants. Analysis of the data revealed that the patient's average age was 43.1 ± 10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95 ± 10.04 out of a maximal 50. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46 ± 1.57 , desire 3.12 ± 1.47 , arousal 2.95 ± 2.17 , lubrication 2.39 ± 2.29 , orgasm 2.82 ± 2.29 , and pain 2.21 ± 2.46 . Though these numbers were reported in the study, data on test population controls were not provided.

A post hoc exploration of the data suggested the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med. 2011 Dec;8 (12):3379-88. Epub 2011 Jun 23.

Wierckx et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with three self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic (Ghent, Belgium). Investigators used the Dutch version of the SF-36 with 36 questions, eight subscales, and two domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self-designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were recruited; ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the one year window. The age of patients was: 30 ± 8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ± 8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oophorectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metoidioplasty ($n=9$; 18.4%), phalloplasty ($n=8$ after metoidioplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device ($n=32$; 65.3%). All had started hormonal therapy at least two years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1 ± 20.7 versus 71.9 ± 18.3 and 72.6 ± 19.2 versus 79.3 ± 16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

c. Observational, surgical patients, cross-sectional, with controls

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery.

The mean age for each of these cohorts was: 50 years (no standard deviation [S.D.]) only reassignment surgery, 51 years (no S.D.) only facial surgery, 49 years (no S.D.) both types of surgery, and 46 years (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than one year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within one standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within one standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a single center (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post- surgical cohorts. Patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Körpers (FBek) which contained three domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0 ± 11.3 years; post-operative 38.2 ± 9.0 years. The mean duration after reassignment surgery was 51 ± 25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0 ± 3.8 versus 5.1 ± 3.7 ; male-to-female 8.1 ± 4.5 versus 4.7 ± 3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1 ± 2.9 versus 8.9 ± 3.1 ; male-to-female 7.0 ± 2.9 vs 9.5 ± 2.6 .

Mate-Kole et al. conducted a single site (London, United Kingdom) prospective non-blinded, observational study using a cross-sectional design and two psychological tests (one with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients from Charing Cross Hospital. The mean ages of the three cohorts were as follows: 34 years for patients undergoing evaluation; 35 years for wait-listed patients; and 37 years for post-operative patients. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, while 14% in each cohort, respectively, had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were statistically higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessiveness) were statistically lower in the post-operative cohort than in the other two cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The Bem Sex Role Inventory femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy non-transgender volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation.

The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 years (range 29- 67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinic (Bern, Switzerland), and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality of life assessment tools included a VAS and the King's Health Questionnaire (KHQ), which consists of eight domains with scores between zero and five or one and five, with lower scores indicating higher preference. The KHQ and the numerical change/difference required for clinical significance (≥ 5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex. No corroborative gynecologic or urologic evaluations were undertaken.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of this study was 51 years (range 39-62 years). The patients had undergone a median of nine surgical procedures in comparison to the two undergone by controls. Reassignment patients were less likely to be married (23.6% versus 65%; $p=0.002$); partnership status was unknown in five patients. The scores of VAS global satisfaction (maximal score eight) were lower for surgically reassigned patients (4.49 ± 0.1 SEM) than controls (7.35 ± 0.26 SEM) ($p<0.0001$).

The abstract stated that quality of life was lower in reassignment patients 15 years after surgery relative to controls. One table in the study, Table 2, delineated statistically and biologically significant differences for four of the eight KHQ domains between the patients and controls: physical limitation: 37.6 ± 2.3 versus 20.9 ± 1.9 ($p<0.0001$), personal limitation: 20.9 ± 1.9 versus 11.6 ± 0.4 ($p<0.001$), role limitation: 27.8 ± 2.4 versus 34.6 ± 1.7 ($p=0.046$), and general health: 31.7 ± 2.2 versus 41.0 ± 2.3 ($p<0.02$). There is a related paper by Kuhn

Printed on 11/17/2016. Page 28 of 150

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a single-center (Oslo, Norway) partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by two senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre- surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post-surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34 ± 9.5 years and female-to-male 33.3 ± 10.0 years. The other control group consisted of patients with personality disorder. Of these, 101 (27 men (33.9 ± 7.3 years) and 74 women (31.6 ± 8.2)) were tested during a treatment program. One year later, 98% were evaluated. A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post-reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7 ± 1 . The Global Assessment of Function was higher (better) in the gender dysphoric groups (78.0 ± 8.9) than in the personality disorder cohort (53.0 ± 9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67 ± 0.57 and 0.56 ± 0.45 . Although they were nominally higher than the healthy normative controls (males: 0.32 ± 0.36 and females 0.41 ± 0.43), they were well within the non- pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without GRS), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50 ± 10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

d. Observational, surgical patients, longitudinal, with controls

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One.* 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed conditions such as, but not limited to, mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were the 2002 WPATH criteria and included evaluation and treatment by one of six specialized teams, name change, a new national identity number indicative of gender, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided.

Investigators identified 804 patients with gender identity disorder (or some other disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3 ± 8.7 (range 20–62) and 36.3 ± 10.1 (range 21–69) years, respectively. Immigrant status was two times higher in reassigned patients ($n=70$, 21.6%) than in either type of control (birth [natal] sex matched $n=294$ [9.1%] or reassigned gender matched $n=264$ [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients ($n=151$ [57.8%]) than in either type of control (birth sex matched $n=1,725$ [61.5%] or reassigned gender matched $n=1804$ [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients ($n=58$, 17.9%) than in either type of control (birth sex matched $n=123$ [3.8%] or reassigned gender matched $n=114$ [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery ($n=27$ [8.3%]) than in controls (hazard ratio 2.8 [CI 1.8–4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. Survival rates at 20 year follow-up (as derived from figure 1) were: female control 97%, male controls 94%, female-to-male patients 88%, and male-to-female patients 82%. The major contributor to this mortality difference was completed suicide ($n=10$ [3.1%]; adjusted hazard ratio 19.1 [CI 5.8–62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients ($n=9$ [2.8%]) than in controls (hazard ratio 2.5 [CI 1.2–5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery ($n=29$ [9.0%]) than in controls (adjusted hazard ratio 4.9 [CI 2.9–8.5]). Male-to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons $n=64$ [20.0%] than in controls (hazard ratio 2.8 [CI 2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landén et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with "regret" in a national database. This same group (Landén et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra- group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least one year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After two years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures (Dhejne et al., 2011). Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real- life experience phase, and family support.

There were 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6). The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.8% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7) had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female-to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. This number appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense (usually in Thailand or the U.S.). This cohort (6% of 681) includes one person who was denied reassignment surgery by Sweden.

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting the diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex- reassignment surgery outside of Sweden (36 of these 41 had surgery after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male (n=5): male-to-female (n=10) ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger at the time of initial surgical application (median age 22 years) than the complete female-to-male cohort at the time of surgical application (median age 27 years). By contrast the male-to-female applicants for reversal were older at the time of initial surgical application (median age 35 years) than the complete male-to-female cohort at the time of initial surgical application (median age 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landén et al. extracted data from medical records and government verdicts. Pearson Chi-square testing with Yates' correction for small sample sizes was used to identify candidate variables predictive of regret. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. Univariate regression analyses further clarified the most important variables. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional multivariate regression analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables had a more than additive effect.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and most of the Dhejne (2014) population. There is a related paper by Landén et al. 1998b that included the criteria to qualify for surgical intervention at that time.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with eight subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty-six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% for the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3 ± 32.4 . The respective scores for the various gender dysphoric cohorts were 157.7 ± 49.8 at initial presentation, 119.7 ± 32.1 after hormone therapy, and 127.9 ± 37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Kockott and Fahrner conducted a single center (Munich, Germany) prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument developed according to the scale used by Hunt and Hampson (1980) for assessment of 17 post-operative patients. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5 ± 13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7 ± 10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3 ± 9.4 years. The age of the patients who were no longer interested in surgery was 31.8 ± 6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score within each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences between groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in
Printed on 11/17/2016. Page 35 of 150

psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a single-center (Baltimore, Maryland, U.S.) prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least one year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive two to four hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score. The score value or the change score that was considered to be biologically significant was not pre-specified in the methods.

The clinic opened with 100 patients, but when the follow-up was completed, 52 patients were interviewed and 50 gave consent for publication. Of these, 15 (four female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (one female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (five female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 33% had some type of psychiatric contact prior to the initial clinic evaluation and 8% had psychiatric contact during the follow-up. Of the patients who had not undergone surgery or who had done so later, 72% had some type of psychiatric contact prior to the initial clinic evaluation and 28% had psychiatric contact during follow-up. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. The absolute score value at follow-up was the same for both groups (1.07+1.53 and 1.10+1.97 respectively). By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere. The absolute score value at follow-up was 0.21+1.89.

Related papers include Meyer et al. (1971), Meyer et al. (1974a-d), and Derogatis et al. (1978) along with commentary response by Fleming et al. (1980).

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. single-center (Belgrade, Yugoslavia) conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator- designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least six months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least one year and sexual orientation to non-natal sex. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 34 were eligible for the study and 32 participated in the study (two were lost to follow-up and four were in the peri-operative period) - 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ± 13.4 months (range 6 months to 4 years). The age was female-to-male 27.8 ± 5.2 (range 23-37) and male-to-female 26.4 ± 7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and eight (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Rupp and Pfafflin conducted a single-center (Ulm, Germany) partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results. Changes or inter-group differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included.

Overall, 140 patients received recruitment letters and then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2 ± 5.78 years (female-to-male) and 52.9 ± 10.82 years (male-to-female). The intervals for follow-up were 14.1 ± 1.97 years and 13.7 ± 2.17 years, respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oophorectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty. Of male-to-female patients, 94.3% had undergone vaginoplasty and perhaps an additional procedure (breast augmentation, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35 ± 0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not being in a steady relationship. Regular sexual relationships were reported by 57.1% of 35 female- to-male respondents and 39.4% of 33 male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. The effect size was statistically significant and large only for the "Interpersonal Sensitivity" scale (one of 10 parameters). The absolute magnitude of mean change was small: from 0.70 ± 0.67 to 0.26 ± 0.34 (scale range 0-4). The duration of follow-up did not correlate with the magnitude of change on the various scales. Differences in baseline SCL-90R scores of 62 participants were compared with the score of 63 of the 69 eligible recruits who declined to enter the study and were notable for higher "Depression" scores for the latter.

Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. The effect size was statistically significant and large only for the "Overly Accommodating" scale (one of eight parameters). The absolute magnitude of mean change was small: from 11.64 ± 5.99 to 7.04 ± 4.73 (scale range 0-32). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was statistically significant and large only for the "Life Satisfaction" scale (one of 12 parameters). The absolute magnitude of mean change was substantive: from 4.43 ± 2.99 to 8.31 ± 2.63 (scale range 0-12). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female to male patients and 19 of 35 male to female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

This current report is an update of prior publications by Pfafflin including work with Junge which was published in a variety of formats and initially in German.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a single-center (Amsterdam, Netherlands) prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigators assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post- surgery data were acquired at least one year post reassignment surgery.

Three hundred twenty five consecutive adolescents and adults were screened for the study. One-hundred three (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy.

Subsequently, the study analysis was limited to adults. One hundred sixty-two (58 [38.9%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing and remained in the normal range after surgery. SCL global scores for psycho- neuroticism were minimally elevated before surgery 143.0 ± 40.7 (scoring range 90 to 450) and normalized after surgery 120.3 ± 31.4 . (An analysis using patient level data for only the completers was not conducted.)

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to- female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed) and Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed)

Udeze et al. conducted a single-center (Leicester, United Kingdom) prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within six months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33 ± 13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

e. Randomized, surgical patients, longitudinal, with controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole et al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic (London, United Kingdom). Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥ 2 year desire to change gender, a ≥ 1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at six months for diagnostic confirmation and exclusion of psychosis.

Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity.

The mean age and range of the entire cohort was 32.5 years (21-53). Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms (Birchnell et al. 1988). Over the two year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic range for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior two years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the two cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities.

2. External Technology Assessments

- a. CMS did not request an external technology assessment (TA) on this issue.
- b. There were no AHRQ reviews on this topic.
- c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

There were two publications in the COCHRANE database, and both were tangentially related. Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.
Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations
Boehmer U. *Am J Public Health*. 2002; 92: 1125–30.

“Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking.”

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

“Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed.”

- e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

*Tech Brief Series: Transgender Re-assignment Surgery Day P. NZHTA Report. February 2002;1(1).
http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf*

The research questions included the following:

1. Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists?

2. If there is evidence of effectiveness, what subgroups would benefit from GRS?"

The authors concluded that there was not enough evidence to answer either of the research questions.

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document: Health Care for Transgender Individuals: Committee Opinion
Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gynecol. 2011;118:1454-8.

"Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. Arch Sex Behav. 2012; 41:759-96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RCTs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial.”

[G] Other. Opinion-like essays, case reports, and other reports not categorized above.”

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. J Clin Endocrinol Metab. 2009; 94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

“This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low.”

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K. www.wpath.org/_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf *Int J Transgend.* 2011;13:165–232.

The WPATH is “an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health.”

WPATH reported, “The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person’s gender identity and that person’s sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).”

The WPATH standards of care (SOC) “acknowledge the role of making informed choices and the value of harm-reduction approaches.”

The SOC noted, “For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.”

e. American Psychological Association

Suggested citation until formally published in the American Psychologist: American Psychological Association. (2015): *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People Adopted by the Council of Representatives, August 5 & 7, 2015*. www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. <http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx>

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and

monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination.”

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013.
http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LGBT research Coordinating Committee noted that most of the health research for this set of populations is “focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism.”

6. Pending Clinical Trials

ClinicalTrials.gov

There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies either took place in or a suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as “clients” instead of “patients,” and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire).

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS’ experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: <https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n#Results>

a. Initial Comment Period: December 3, 2015 – January 2, 2016

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups.

b. Second Comment Period: June 2, 2016 – July 2, 2016

During the second 30-day public comment period, we received a total of 45 public comments, 7 of which were not posted on the web due to personal health information content. Overall, 82% supported coverage of gender reassignment surgery, 11% opposed, and 7% were neutral or silent in their comment whether they supported or opposed coverage. Half of the comments were submitted by individuals who expressed support for coverage of gender reassignment surgery (51%). We also received comments from physicians, providers, and other health professionals who specialize in healthcare for transgender individuals (17%). We received one comment from a municipality, the San Francisco Department of Public Health. Associations (American Medical Association, American College of Physicians, American Academy of Nursing, American Psychological Association, and LGBT PA Caucus) and advocates (Center for American Progress with many other signatories, Jamison Green & Associates) also submitted comments.

Below is a summary of the comments CMS received. In some instances, commenters identified typographical errors, context missed, and opportunities for CMS to clarify wording and classify articles for ease of reading in the memorandum. As noted earlier, when appropriate and to the extent possible, we updated the decision memorandum to reflect those corrections, improved the context, and clarified the language. In light of public comments, we re-evaluated the evidence and our summaries. We updated our summaries of the studies and clarified the language when appropriate.

1. Contractor Discretion and National Coverage Determination

Comment: Some commenters, including advocates, associations, and providers, supported CMS' decision for MAC contractor discretion/case-by-case determination for gender reassignment surgery. One stakeholder stated, "We agree with the conclusion that a NCD is not warranted at this time."

Response: We appreciate the support and understanding among stakeholders for our proposed decision to have the MACs determine coverage on a case-by-case basis. We have clarified in this final decision memorandum that

coverage is available for gender reassignment surgery when determined reasonable and necessary and not otherwise excluded by any other relevant statutory requirements by the MAC on a case-by-case basis. "The case-by-case model affords more flexibility to consider a particular individual's medical condition than is possible when the agency establishes a generally applicable rule." (78 Fed. Reg. 48165 (August 7, 2013)).

Comment: Some commenters cautioned that CMS' choice to not issue a NCD at this time must not be interpreted as a national non-coverage determination or used in any way to inappropriately restrict access to coverage for transgender Medicare beneficiaries or other transgender individuals. Multiple commenters indicated their disappointment that CMS did not propose a National Coverage Determination (NCD) and, instead, chose to continue to have local MACs make the coverage decisions on a case-by-case basis. Commenters stated this could result in variability in coverage.

Response: We appreciate the comments. We are not issuing a NCD at this time because the available evidence for gender reassignment surgery provides limited data on specific health outcomes and the characteristics of specific patient populations that might benefit from surgery. In the absence of a NCD, the MAC's use the same statutory authority as NCDs, section 1862(a)(1)(A) of the Social Security Act (the Act). Under section 1862(a)(1)(A) an item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. While CMS did not have enough evidence to issue a NCD, we believe the MACs will be able to make appropriate coverage decisions on a case-by-case basis taking into account individual characteristics of the Medicare beneficiary.

Comment: Some commenters sought a NCD that would establish guidelines for coverage and include elements such as a prescribed set of surgeries and a shared decision making element.

Response: For the reasons stated above, we are not issuing a NCD at this time and, therefore, are not establishing specific gender reassignment surgery coverage guidelines for the Medicare program. We generally agree that shared decision-making is a fundamental approach to patient-centered health care decisions and strongly encourage providers to use these types of evidence based decision aids. We have not found a shared decision aid on GRS and encourage the development of this necessary element to conduct formal shared-decision making.

Comment: Some commenters expressed concern that there is a misunderstanding of transgender individuals as having a disorder or being abnormal. Some commenters indicated a history of bias and discrimination within society as a whole that has occurred when transgender individuals have sought health care services from the medical community. Some commenters are concerned that the decision not to make a NCD will subject individuals seeking these services to corporate bias by Medicare contractors.

Response: We acknowledge the public comments and that there has been a transformation in the treatment of individuals with gender dysphoria over time. In this NCA, we acknowledge that gender dysphoria is a recognized Diagnostic and Statistical Manual of Mental Disorders (DSM) condition. With respect to the concern about potential bias by Medicare contractors, we have no reason to expect that the judgments made on specific claims will be influenced by an overriding bias, hostility to patients with gender dysphoria, or discrimination. Moreover, the Medicare statute and our regulations provide a mechanism to appeal an adverse initial decision if a claim is denied and those rights may include the opportunity for judicial review. We believe the Medicare appeals process would provide an opportunity to correct any adverse decision that was perceived to have been influenced by bias.

Comment: Commenters mentioned the cost of gender reassignment surgery could influence MAC decision making.

Response: The decisions on whether to cover gender reassignment surgery in a particular case are made on the basis of the statutory language in section 1862 of the Social Security Act that establish exclusions from coverage and would not depend on the cost of the procedure.

2. Coverage with Evidence Development and Research

Comment: In our proposed decision memorandum, we specifically invited comments on whether a study could be developed that would support coverage with evidence development (CED). One organization commented, "We strongly caution against instituting a CED protocol." Commenters were opposed to coverage limited in clinical trials, suggesting that such coverage would restrict access to care. Several commenters provided suggested topics for clinical research studies for the transgender population. For example, one commenter suggested a study of non-surgical treatment for transgender children prior to puberty.

Response: While we appreciate the comments supporting further research, in general, for gender reassignment surgery, we agree that CED is not the appropriate coverage pathway at this time. While CED is an important mechanism to support research and has the potential to be used to help address gaps in the current evidence, we are not aware of any available, appropriate studies, ongoing or in development, on gender reassignment surgery for individuals with gender dysphoria that could be used to support a CED decision.

3. Gender Reassignment Surgery as Treatment

Comment: One group of commenters requested that CMS consider that, “The established medical consensus is that GRS is a safe, effective, and medically necessary treatment for many individuals with gender dysphoria, and for some individuals with severe dysphoria, it is the only effective treatment.”

Response: We acknowledge that GRS may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a NCD that identifies the precise patient population for whom the service would be reasonable and necessary.

4. Physician Recommendations

Comment: Several commenters stated that gender reassignment surgery should be covered as long as it was determined to be necessary, or medically necessary by a beneficiary’s physician.

Response: Physician recommendation is one of many potential factors that the local MAC may consider when determining whether the documentation is sufficient to pay a claim.

5. WPATH Standards of Care

Comment: Several commenters suggested that CMS should recommend the WPATH Standards of Care (WPATH) as the controlling guideline for gender reassignment surgery. They asserted it could satisfy Medicare’s reasonable and necessary criteria for determining coverage on a case-by-case basis.

Response: Based on our review of the evidence and conversations with the experts and patient advocates, we are aware some providers consult the WPATH Standards of Care, while others have created their own criteria and requirements for surgery, which they think best suit the needs of their patients. As such, and given that WPATH acknowledges the guidelines should be flexible, we are not in the position to endorse exclusive use of WPATH for coverage. The MACs, Medicare Advantage plans, and Medicare providers can use clinical guidelines they determine useful to inform their determination of whether an item or service is reasonable and necessary. When making this determination, local MACs may take into account physician’s recommendations, the individual’s clinical characteristics, and available clinical evidence relevant to that individual.

6. Scope of the NCA Request

Comment: One commenter stated that CMS did not address the full scope of the NCA request.

Response: The formal request for a NCD is publicly available on our tracking sheet. (<https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id282.pdf>) The letter did not explicitly seek a national coverage determination related to counseling or hormone therapies, but focused on surgical remedies. CMS is aware that beneficiaries with gender dysphoria use a variety of therapies.

Comment: Other commenters stated the scope of the proposed decision is unnecessarily broad because it discussed therapies other than surgery. They suggested this discussion could lead to the unintended consequence of restricting access to those services for transgender Medicare beneficiaries and other transgender individuals.

Response: As we noted in our proposed decision, our decision focused only on gender reassignment surgery. In the course of reviewing studies related to those surgeries, occasionally authors discussed other therapies that were mentioned in our summaries of the evidence. To the extent possible, we have modified our decision to eliminate the discussion of other therapies which were not fully evaluated in this NCA.

7. NCA Question

Comment: Some commenters expressed concern about the phrasing of the question in this NCA.

Response: The phrasing of the research question is consistent with most NCAs and we believe it is appropriate.

8. Evidence Summary and Analysis

Comment: Several commenters disagreed with our summary of the clinical evidence and analysis. A few commenters contended that the overall tone of the review was not neutral and seemed biased or flawed. One commenter noted that the Barrett publication was available on the Internet.

Response: We appreciate the comments that identified technical errors, and we made the necessary revisions to this document. However, we disagree with the contention that our evidence review was not neutral and seemed biased or flawed. We believe that the summary and analysis of the clinical evidence are objective. As with previous NCAs, our review of the evidence was rigorous and methodical. Additionally, we reviewed the Barrett publication, but it did not meet our inclusion criteria to be included in the Evidence section.

9. Evidence Review with Transgender Experts

Comment: Several commenters requested that CMS re-review the clinical evidence discussed in the proposed decision memorandum with outside experts in the field of transgender health and transition/gender reassignment-related surgeries. Several offered the expertise within their organization to assist in this effort.

Response: We appreciate these comments and the transgender health community's willingness to participate. For this NCA we discussed gender reassignment surgery protocols with experts, primarily in coordinated care settings. Additionally, the public comment periods provide opportunities for expert stakeholder input. According to our process for all NCAs, we do not jointly review evidence with external stakeholders but have carefully reviewed the very detailed comments submitted by a number of outside experts in transgender health care.

10. Previous Non-Coverage NCD

Comment: One commenter noted that they thought research studies for gender reassignment surgery could not take place when the old NCD that prohibited coverage for gender reassignment surgery was in effect.

Response: CMS does not directly conduct clinical studies or pay for research grants. Some medical services are non-covered by Medicare; however, national non-coverage does not preclude research via a number of avenues and other funding entities such as the National Institutes of Health. In this instance, the previous NCD did not preclude interested parties from funding research for gender reassignment surgery that could have been generalizable to the Medicare population.

11. How the Medicare Population Differs from the General Population

Comment: One commenter questioned how the Medicare population differed from the general population, and why any differences would be important in our decision-making.

Response: The Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues.

12. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Comment: One commenter suggested CMS should have convened a MEDCAC for this topic.

Response: We appreciate the comment. Given the limited evidence, we did not believe a MEDCAC was warranted according to our guidance document entitled "Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee" (<https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html>).

13. §1557 of the Affordable Care Act (ACA)

Comment: Some commenters asserted that by not explicitly covering gender reassignment surgery at the national level, CMS was discriminating against transgender beneficiaries in conflict with Section 1557 of the Affordable Care Act (ACA).

Response: This decision does not affect the independent obligation of covered entities, including the Medicare program and MACs, to comply with Section 1557 in making individual coverage decisions. In accordance with Section 1557, MACs will apply neutral nondiscriminatory criteria when making case-by-case coverage determinations related to gender reassignment surgery.

14. Medicaid

Comment: Some commenters observed that some states cover gender reassignment surgery through Medicaid or require commercial insurers operating in the state to cover the surgery.

Response: We appreciate the information about Medicaid and state requirements; however, State decisions are separate from Medicare coverage determinations. We make evidence-based determinations based on our statutory standards and processes.

15. Commercial Insurers

Comment: In several instances, commenters told us that the healthcare industry looks to CMS coverage determinations to guide commercial policy coverage.

Response: CMS makes evidence-based national coverage determinations based on our statutory standards and processes as defined in the Social Security Act, which may not be the same standards that are used in commercial insurance policies or by other health care programs. In addition as noted above, the Medicare population is different (e.g., Medicare covers 95% of adults 65 and older) than the typical population under

16. Healthcare for Transgender Individuals

Comment: Numerous professional associations wrote to CMS to explain their support for access to healthcare for transgender individuals.

Response: CMS recognizes that transgender beneficiaries have specific healthcare needs. Many health care treatments are available. We encourage all beneficiaries to utilize their Medicare benefits to help them achieve their best health.

17. Intended Use of the Decision Memorandum

Comment: Several commenters expressed concern that the analysis provided in the proposed and final decision memorandums may be used by individuals, entities, or payers for purposes unrelated to Medicare such as denial of coverage for transgender-related surgeries.

Response: The purpose of the decision memoranda is to memorialize CMS' analysis of the evidence, provide responses to the public comments received, and to make available the clinical evidence and other data used in making our decision consistent with our obligations under the § 1862 of the Act. The NCD process is open and transparent and our decisions are publicly available. Congress requires that we provide a clear statement of the basis for our determinations. The decision memoranda are an important part of the record of the NCD. Our focus is the Medicare population which, as noted above, is different than the general population in a number of ways. Other entities may conduct separate evidence reviews and analyses that are suited for their specific populations.

18. Cost Barriers to Care and Effects

Comment: A few commenters stated that without Medicare coverage, surgery is difficult to afford and there may be a risk of negative consequences for the individual. One commenter suggested that CMS should consider prior-authorization for these surgeries.

Response: CMS is aware that paying out-of-pocket for medical care is a strain on a beneficiary's finances. We are also aware of beneficiaries' hesitancy to undergo surgery prior to knowing whether or not Medicare will pay the claim. Gender reassignment surgeries are not the only procedures whereby payment is not determined until after the provider submits the claim to Medicare. Importantly, documentation for the claims need to be explicit about what procedures were performed and include the appropriate information in the documentation to justify using the code or codes for surgery. Of note, CMS has claims data that indicate Medicare has paid for gender reassignment surgeries in the recent past. Determining which services are designated for prior-authorization is outside of the scope of the NCA process.

19. Surgical Risks and Benefits

Comment: A number of commenters conveyed the benefits of gender reassignment surgery, while other commenters expressed concern that gender reassignment surgery was harmful.

Response: We appreciate these comments.

20. Expenditure of Federal Funds

Comment: Some commenters opposed spending Medicare program funds on gender reassignment surgery for a variety of reasons. For example, some commenters believe it is an "elective" procedure. Other commenters suggested that funds should first be spent on other priorities such as durable medical equipment (DME) or mobility items such as power chairs; increasing reimbursement to providers; or that spending should be limited to the proportion to the transgender adult population in the Medicare program.

Response: The purpose of this NCA is to determine whether or not CMS should issue a NCD to cover surgery for patients who have gender dysphoria. NCAs do not establish payment amounts or spending priorities and, therefore, these comments are outside the scope of this consideration.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage.

Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.” *Heckler v. Ringer*, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

CMS carefully considered all the studies listed in this decision memorandum to determine whether they answered the question posed in this NCA. While there appears to be many publications regarding gender reassignment surgery, it became clear that many of the publications did not meet our inclusion/exclusion criteria as explained earlier in the decision memorandum.

Thirty-three papers were eligible based on our inclusion/exclusion criteria for the subsequent review (Figure 1). All studies reviewed had potential methodological flaws which we describe below.

A. Quality of the Studies Reviewed

Overall, the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding (a situation where the association between the intervention and outcome is influenced by another factor such as a co-intervention), small sample sizes, lack of validated assessment tools, and considerable lost to follow-up (Appendices C and F). The impact of a specific therapeutic intervention can be difficult to determine when there are multiple serial treatments such as psychotherapy, hormone treatment and surgery. To reduce confounding, outcome assessment just prior to and after surgery such as in a longitudinal study would be helpful. The objective endpoints included psychiatric treatment, attempted suicide, requests for surgical reversal, morbidity (direct and indirect adverse events), and mortality (Appendix F). CMS agrees with the utility of these objective endpoints. Quality of life, while important, is more difficult to measure objectively (Appendix E).

Of the 33 studies reviewed, published results were conflicting – some were positive; others were negative. Collectively, the evidence is inconclusive for the Medicare population. The majority of studies were non-longitudinal, exploratory type studies (i.e., in a preliminary state of investigation or hypothesis generating), or did not include concurrent controls or testing prior to and after surgery. Several reported positive results but the potential issues noted above reduced strength and confidence. After careful assessment, we identified six studies that could provide useful information (Figure 1). Of these, the four best designed and conducted studies that assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies did not demonstrate clinically significant changes or differences in psychometric test results after GRS. (Heylens et al., 2014; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008) (Appendix C Panel A and Appendix G.)

Two studies (three articles) assessed functional endpoints (request for surgical reassignment reversal and morbidity/mortality) (Dhejne et al., 2011; Dhejne et al., 2014 along with Landén et al., 1998) (Figure 1 and Appendix C, Panel A and Appendix G). Although the data are observational, they are robust because the Swedish national database is comprehensive (including all patients for which the government had paid for surgical services) and is notable for uniform criteria to qualify for treatment and financial coverage by the government. Dhejne et al. (2014) and Landén et al. (1998) reported cumulative rates of requests for surgical reassignment reversal or change in legal status of 3.3% while Dhejne et al. (2014) reported 2.2%. The authors indicated that the later updated calculation had the potential to be an underestimate because the most recent surgical cohorts were larger in size and had shorter periods of follow-up.

Dhejne et al., (2011) tracked all patients who had undergone reassignment surgery (mean age 35.1 years) over a 30 year interval and compared them to 6,480 matched controls. The study identified increased mortality and psychiatric hospitalization compared to the matched controls. The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. We note, mortality from this patient population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Further, we cannot exclude therapeutic interventions as a cause of the observed excess morbidity and mortality. The study, however, was not constructed to assess the impact of gender reassignment surgery *per se*.

We believe at minimum study designs should have a pre-test/post-test longitudinal design accompanied by characterization of all patients lost to follow-up over the entire treatment series as well as those patients who did not complete questionnaires, and the use of psychometric quality-of-life tools which are well validated with linkage to “hard” (objective) patient outcomes in this particular patient population (Trentacosti 2007, PRO 2009) (Appendices C and D).

Patient Care

Clinical evidentiary questions regarding the care of patients with gender dysphoria remain. Many of the publications focused on aspects of surgical technique as opposed to long-term patient outcomes. The specific type(s) of gender/sex reassignment surgery (e.g., genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific types of surgical procedures under study. Furthermore, surgical techniques have changed significantly over the last 60 years and may not reflect current practice (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations present a general framework and guidance on the care of the transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH notes, “More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.” Appendix D in the WPATH Standards of Care briefly describes their evidence base and acknowledges the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care rather than gender reassignment surgery was often the main focus. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

Psychometric Tools

CMS reviewed psychometric endpoints because gender dysphoria (inclusive of prior nomenclature) describes an incongruence between the gender assigned at birth and the gender(s) with which the person identifies.

The psychometric tools used to assess outcomes have limitations. Most instruments that were specific for gender dysphoria were designed by the investigators themselves or by other investigators within the field using limited populations and lacked well documented test characterization. (Appendices E and F) By contrast, test instruments with validation in large populations were non-specific and lacked validation in the gender dysphoric patient populations. (Appendices E and F). In addition, the presentation of psychometric results must be accompanied by enough information about the test itself to permit adequate interpretation of test results. The relevant diagnostic cut-points for scores and changes in scores that are clinically significant should also be scientifically delineated for interpretation.

Generalizability

It is difficult to generalize these study results to the current Medicare population. Many of the studies are old given they were conducted more than 10 years ago. Most of these studies were conducted outside of the U.S. in very different medical systems for treatment and follow-up. Many of the programs were single-site centers without replication elsewhere. The study populations were young and without significant physical or psychiatric co-morbidity (Appendix D). As noted earlier, psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landén et al., 1998).

Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. This review has identified gaps in the evidentiary base as well as recommendations for good study designs. The Institute of Medicine, the National Institutes of Health, and others also identified many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps. These gaps have been delineated as they represent areas in which patient care can be optimized and are opportunities for much needed research.

B. Health Disparities

Four studies included information on racial or ethnic background. The participants in the three U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants

in the single Asian study were Chinese (Liao, 1993). Additional research is needed in this area.

C. Summary

Based on an extensive assessment of the clinical evidence as described above, there is not enough high quality evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively.

The knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines. Additional research of contemporary practice is needed. To assess long-term quality of life and other psychometric outcomes, it will be necessary to develop and validate standardized psychometric tools in patients with gender dysphoria. Further, patient preference is an important aspect of any treatment. As study designs are completed, it is important to include patient-centered outcomes.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We have received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination on whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery would be reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination relating to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 <i>Chapter: Psychosexual Disorders</i>	<i>Trans-sexualism</i> <i>302.5x [Gender Identity Disorder of Child-hood (302.6)]</i>	Required A (cross- gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III-Revised 1987 <i>TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence</i>	Trans-sexualism (TS) (302.50) <i>[GID of C]</i>	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1° and 2° sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-transsexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood , non-trans-sexual type, added			
DSM IV 1994 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex •Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM IV-Revised 2000 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6

DSM Version	Condition Name	Criteria	Criteria	Comments
			•e.g., frequent passing as the other sex - Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex - Clinically significant distress or impairment in social, occupational, or other important areas of functioning	•e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 <i>Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders</i>	Gender Dysphoria (302.85)	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	•Marked discordance between natal 1^o and 2^o sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1^o and 2^o sex characteristics** •Marked desire to acquire 1^o and 2^o sex characteristics of the other sex (or some alternative gender) - Clinically significant distress or impairment in social, occupational, or other important areas of functioning * or in young adolescents, the anticipated 2^o sex characteristics ** or in young adolescents, prevent the development of the anticipated 2^o sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: •Strong desire to be of the other gender or an insistence that one is of another gender.	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

DSM Version	Condition Name	Criteria	Criteria	Comments
			•Strong preference for cross-gender roles in make-believe play. •Strong preference for the toys, games, or activities of the other gender. •Strong preference for playmates of the other gender. •In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing •In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1^o=primary 2^o=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	804 w GD	324	324 (100%)	-
Dhejne 2014 Landén	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 50 were excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, & 16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1 & 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional		40	10 (25%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	Controlled	14 excluded for demographic matching reasons			The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual relationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender identity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional		119	119 (100%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.			Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results ¹⁰³ .
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal		1331	1177 (88.4%)	-

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No analysis by tx status	The number in the available patient pool was not specified.			
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference

B/C=because

BSRI=Bem Sex Role Inventory

F=Female

FP-R=Freiberg Personality Inventory

GD=Gender dysphoria

GID=Gender identity disorder

HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems

M=Male

NA=Not applicable

SCL-90=Symptom Checklist-90

SF-36=Short Form 36

GRS=Sex reassignment surgery

Tx=Treatment

W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery: 50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian

Author	Age (years, mean, S.D., range)	Gender	Race
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3±8.7 (20-62), M to F 36.3±10.1(21-69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landén	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7±4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M to F; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).		-

Author	Age (years, mean, S.D., range)	Gender	Caucasian
		W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio 1:1.6.	
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F to M: 27.8 (18–46), M to F 37.3 (21–60). Time of GRS: F to M: 31.4 (22–49), M to F 38.2 (22–57). Time of follow-up for post-GRS: F to M: 38.9 (28–53), M to F 46.0 (25–69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve <i>Smilkstein</i>	Published in 1978 Initial data: 152 families in the U.S. A “friends” component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory <i>Beck, Ward, Mendelson, Mock, & Erbaugh</i>	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. It is copyrighted and requires a fee for use
Bem Sex Role Inventory <i>Bem</i>	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire <i>Clement & Lowe</i>	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale <i>Lindgren & Pauly</i> <i>(Kuiper, Dutch adaptation 1991)</i>	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire)	Developed circa 1966 Manual published 1970

Instrument Name and Developer	Development and Validation Information
<i>Crown & Crisp</i>	Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey <i>Anderson, Mikulić, Vermeylen, Lyly-Yrjanainen, & Zigante,</i>	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index <i>Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen</i>	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Körpers <i>Strauss</i>	Published 1996 (German)
Freiberg Personality Inventory <i>Fahrenberg, Hampel, & Selg</i>	7 th edition published 2001, 8 th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" <i>Smith, van Goozen, Kuiper, & Cohen-Kettenis</i>	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale <i>Altstotter-Gleich</i>	Published 1989 (German)
General Health Questionnaire <i>Goldberg & Blackwell (initial study)</i> <i>Goldberg & Williams (manual)</i>	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale <i>Zigmond & Snaith</i>	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1 st 50 compared to 2 nd 50.
Inventory of Interpersonal Problems <i>Horowitz</i>	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psychotherapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire <i>Kelleher, Cardozo, Khullar, & Salvatore</i>	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory <i>Hathaway & McKinley</i>	Published in 1941 Updated in 1989 with new, larger, more diverse sample.

Instrument Name and Developer	Development and Validation Information
<i>Butcher, Dahlstrom, Graham, & Tellegen</i>	MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphilia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences <i>Wolfradt</i>	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" <i>Cohen-Kettenis & van Goozen</i>	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale <i>Rosenberg</i>	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 <i>RAND</i> <i>Ware & Sherbourne 1992</i> <i>McHorney, Ware, & Raczek 1993</i>	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale <i>Watson & Friend</i>	Initial publication in 1969 Requires permission for use
Social Support Scale <i>Van Tilburg 1988</i>	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire <i>Spielberger, Gorsuch, Lushene, Vagg, & Jacobs</i>	Current format published in 1983 Proprietary test
Symptom Checklist-90 <i>Derogatis, Lipman, Covi</i> <i>Derogatis & Cleary</i>	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale <i>Fitts & Warren</i>	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other information available. Requires qualification for use
Utrecht Gender Dysphoria Scale <i>Cohen-Kettenis & van Goozen</i>	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)

Instrument Name and Developer	Development and Validation Information
WHO-Quality of Life (abbreviated version) <i>Harper for WHO group</i>	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landén	Yes	-	-	-	Includes demographics*	Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS, STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscherman et al.	Yes	-	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2 nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Körpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 ($\pm$ R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.**Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets**

Author	Test	Patient and Data Loss	Results
Psychometric Test			
Heylens et al. Belgium 2014	SCL-90R	90 applicants for SRS were recruited. •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx. •12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical comorbidity, personal decision for no tx, or personal decision for only hormone tx. •1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. •1 (12.2% of initial recruits) had not yet received SRS by study close. 46 (51.1% of recruited) underwent serial evaluation •The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) missing data for another 1.1% to 11.1%.	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.
Ruppin,Pfafflin, Germany 2015	SCL-90R	The number in the available patient pool was not specified.	

Author	Test	Patient and Data Loss	Results
		140 received recruitment letters. •2 (1.4% of those with recruitment letters) had died. •1 (0.7%) was institutionalized. •5 (3.6%) were ill. •8 (5.7%) did not have time. •8 (5.7%) stated that GD was no longer an issue. •8 (5.7%) provided no reason. •28 (20.0%) declined further contact. •9 (6.4%) were lost to follow-up. 71 (50.7%) agreed to participate. •2 (1.4%) had not undergone SRS •The test was not completed by 9. missing data for another 6.4%.	At t=0, the "global severity index "SCL-90R score was 0.53 ± 0.49. At post-SRS follow-up the score had decreased to 0.28 ± 0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70 ± 0.67 at t=0 and 0.26 ± 0.34 post-SRS.
Smith et al. Holland 2005	MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. •103 (31.7%) were not eligible to start hormone tx & real-life experience. •34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. •36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0 ± 40.7. At post SRS-follow-up, the score had decreased to 120.3 ± 31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. •Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.

Author	Test	Patient and Data Loss	Results
			There were no statistically significant changes in the global score or for any of the subscales.
National Databases			
Dehjne Sweden 2011	Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. •480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. •All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9-8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0-3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landén et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. •All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID=NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery
Tx=Treatment [Back to Top](#)

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID:> 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstötter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentität* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid- Technique as shown at the example of the assessment of gender identity], Verlag für empirische Pädagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients.* 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5& 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to- male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry.* 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Gooren LJ, Eklund PC. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism*. 1989 Sep;38(9):869-73. PMID: 2528051.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel- Journeel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 June;328(19):1490-4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA*. 2010 Summer-Fall;22 (4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristoni J, Menggola MC, Jannini EA, Mannelli C, Corona G, Mercurio M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res*. 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013 Mar;13(3):214- 22. Epub 2012 Dec 21. PMID: 23260128.

Barlow DH, Abel GG, Blanchard EB. Gender identity change in transsexuals. Follow-up and replications. *Arch Gen Psychiatry*. 1979 Aug;36(9):1001-7. PMID: 464738.

Barrett J. (1998) *Psychological and social function before and after phalloplasty*. University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or *IJT*. 1998; 2:1 or <http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal..pdf>.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav*. 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav*. 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med* .2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

Baumeister S, Sohn M, Donike C, Exner K. [Phalloplasty in female-to-male transsexuals: experience from 259 cases]. *Handchir Mikrochir Plast Chir.* 2011 Aug;43(4):215-21. Epub 2011 Aug 11. PMID: 21837614.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis.* 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to- female transsexualism. *Fertil Steril.* 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinhaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril.* 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology.* 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg.* 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third> sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol.* 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheoran B, Sheth L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav*. 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes*. 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, management* (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav*. 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry*. 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med*. 2011 Jun 30;364 (26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow- up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25 (3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health.* 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am.* 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med.* 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev*. 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics*. 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav*. 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)*. 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav*. 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth*. 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self- injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med*. 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol*. 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex*. 2006;51(3):53-69. PMID: 17135115.

CMS Office of Minority Health. New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. 2015. Academy Health Annual Research Meeting, Minneapolis, Minnesota.

CMS Office of Minority Health. If You Build It, They Will Come: Accessing and Utilizing HHS LGBTI Data and Information Products. 2015. Gay and Lesbian Medical Association Meeting, Portland, Oregon.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res*. 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT. Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress

in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10. PMID: 25691225.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend*. 2011;13:165-232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from

a household probability sample of adults. *Am J Public Health*. 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol*. 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women's souls: Personal narrative of Thailand's transgendered youth*. Routledge.

Costantino A, Cerpomini S, Alvisi S, Morselli P, Venturini S, Meriggiani M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther.* 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148- 53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry.* 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril.* 2010 Dec;94 (7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. [February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf](http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf).

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav.* 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry.* 2007 Apr;22(3):137- 41. Epub 2006 Dec 26. PMID: 17188846.

Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male- to-female transsexual after initiation of hormone therapy. *J Clin Neurosci.* 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull.* 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci.* 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry.* 1974;7(0):79- 110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol.* 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis.* 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gynecol*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186 (2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6 (2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav*. 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol*. 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male- to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduyn T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*. 2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav*. 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol*. 2011 Jun;51 (2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis*. 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan- Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub*. 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinic D, Barisic V, Djordjevic ML, Vujovic S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal*. 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72 (1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg*. 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20 (6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikulić B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview*. EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrac M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work*. EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Ferring D, Filipp SH. Messung des Selbstwertgefühls: Befunde zu Reliabilität, Validität und Stabilität der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica*. 1996; 42: 284–292. German. (Not in PubMed)

Ferron P, Young S, Boulanger C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med*. 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Flores A, Herman J, Gates G, Brown T. (2016) *How many adults identify as transgender in the United States?* Los Angeles, CA: The Williams Institute.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry*. 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab.* 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexualsurgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir.* 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res.* 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav.* 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl.* 2011 May;13 (3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol.* 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev.* 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol.* 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril.* 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand*. 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165 (4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Gates GJ. How many people are lesbian, gay, bisexual, and transgender? 2011. (Not in PubMed)
williamsinstitute@law.ucla.edu.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNeil D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law*. 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int*. 2007 Sep;100(3):607- 13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website: <http://www.stat.berkeley.edu/users/hhuang/141C-2008.html>. Section Website: <http://www.stat.berkeley.edu/users/mgoldman>.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess*. 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav*. 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav*. 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav*. 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero- Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res.* 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res.* 2005;64 Suppl 2:31-6. PMID: 16286768.

Gooren L. Clinical practice. Care of transsexual persons. *N Engl J Med.* 2011 Mar 31;364(13):1251-7. PMID: 21449788.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia.* 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes.* 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross- sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol.* 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med.* 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia.* 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebieux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med.* 2012 Feb;9 (2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self- esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis.* 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict.* 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res.* 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol.* 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis.* 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment.* 1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonasate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav.* 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and> strength of recommendations. *BMJ.* 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 3;336(7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652):1049-51. Erratum in: *BMJ*. 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011 Apr;64(4):395-400. Epub 2010 Dec 30. PMID: 21194891.

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol*. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol*. 2011 Dec;64(12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian,

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery*. 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand*. 2000 Oct;102(4):276- 81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13 (4):364-8. PMID: 13463138.

Hathaway SR, Reynolds PC, Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hebbar S, Pandey H, Chawla A. Understanding King's Health Questionnaire (KHQ) in assessment of female urinary incontinence. *Int J Res Med Sci* 2015;3:531-8.

Hembree WC, Cohen-Kettenis P, Delamarre-Van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt*. 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res*. 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry*. 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics/objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services. Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology*. 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel)*. 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand*. 1971;47 (1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel)*. 1973;6(2):65- 80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat*. 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21; (1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol*. 1988 Dec;56 (6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci*. 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav*. 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav*. 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile intranssexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B- Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha- reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013.
<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. <http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf>.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex*. 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol*. 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS*. 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltán R, Kawaciuk I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med*. 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav*. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal*. 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab*. 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co- morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hoer C, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav*. 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci*. 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol*. 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics*. 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav*. 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child*. 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav*. 1987 Dec;16(6):511-22. PMID: 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav*. 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences*. Stanford, Calif.: Stanford University Press, 1966.

Krege S, Bex A, Lümnen G, Rübber H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollner H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol*. 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hildebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol*. 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009 Nov;92(5):1685-1689.e3. Epub

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5: DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician*. 2013 Oct 15;88(8):Online. PMID: 24364581.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res*. 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation*. 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet*. 2011 April 9;377: 1211. PMID:2 1481690.

A - Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand*. 1998 Apr;97(4):284-9. PMID: 9570489.

B - Landén M, Walinder J, Lundstrom B. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. *Acta Psychiatr Scand* 1998; 97: 189-194.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol*. 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav*. 1999 Dec;28(6):581-3. PMID: 10650442.

Lawrence A. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav*. 2003 Aug;32(4):299-315. PMID: 12856892.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav*. 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav*. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Arch Sex Behav*. 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoepfner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis*. 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med*. 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract*. 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lief HI, Hubschman L. Orgasm in the postoperative transsexual. *Arch Sex Behav*. 1993 Apr;22 (2):145-55. PMID: 8476334.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav*. 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand*. 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975 Nov;4(6):639-56. PMID: 1212093.

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav.* 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav.* 1979 Sep;8 (5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav.* 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess.* 1984 Oct;48 (5):500-7. PMID: 6389823.

Lundström B, Pauly I, Wålinder J. Outcome of sex reassignment surgery. *Acta Psychiatr Scand.* 1984 Oct;70(4):289-94. PMID: 6388248.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev.* 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D,

Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grütters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab.* 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Matarix-Cole D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav*. 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry*. 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry*. 1990 Aug;157:261-4. PMID: 2224377.

Maycock L, Kennedy H. Breast care in the transgender individual. *J Midwifery Womens Health*. 2014 Jan-Feb;59(1):74-81. Epub 2013 Nov 13. PMID: 24224502.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med*. 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database*. 2009. No.3. www.birmingham.ac.uk/Documents/college-

Medraś M, Józków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol.* 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy.* 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health.* 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self- prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med.* 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Jannini E, Lenzi A, Maggi M, Manieri C. Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. *Eur J Endocrinol.* 2010 May;162(5):831-3. Epub 2010 Feb 11. PMID: 20150325.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl.* 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf).* 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):607- 15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

D- Meyer JK. Clinical variants among applicants for sex reassignment. *Arch Sex Behav*. 1974 Nov;3 (6):527-58. PMID: 4429437.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10 (4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav*. 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Anseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miles C, Green R, Hines M. Estrogen treatment effects on cognition, memory and mood in male-to- female transsexuals. *Horm Behav*. 2006 Dec;50(5):708-17. Epub 2006 Aug 1. PMID: 16884726.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics*. 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient- subjects. *J Med Ethics*. 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol*. 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg*. 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. Spanish. PMID: 22542505.

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med*. 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav*. 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollner H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med*. 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Muller AJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

NIH FY 2016-2020 Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities. 2015 http://edi.nih.gov/sites/default/files/EDI_Public_files/sgm-strategic-plan.pdf

NIH-LGBT 2013: National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care*. 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015*. (Portland State quantitative methods)www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med.* 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. *J Acquir Immune Defic Syndr.* 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health* 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health.* 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery.* New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

Odgaard-Jensen J, Vist GE, Timmer A, Kunz R, Akl EA, Schünemann H, Briel M, Nordmann AJ, Pregno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev.* 2011 Apr 13;(4):MR000012. PMID: 21491415.

O'Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J.* 1981;50 (1):46-9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res.* 2008 Jan 15;157 (1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med.* 2011 Feb;165(2):171-6. PMID: 21300658.

surgical treatment. *World J Psychiatry*. 1996;56(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav*. 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long- term follow-up. *Arch Sex Behav*. 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr*. 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav*. 2011 Apr;15(3):674-82. PMID: 21604064.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex*. 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögenderfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to- male transsexuals. *J Sex Med*. 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res*. 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to- female transsexual persons. *J Voice*. 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology*. 2005 Jul;16 (4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968 Nov;147(5):460- 71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15 (1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril*. 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med*. 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work*. 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 May 23;7:9. PMID: 22621419.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims. December 2009.* <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf>.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To- Male Genital Reconstructive Surgery. *IJT*. 1999 Jul-Sept;3(3). (Not in PubMed) <http://www.symposion.com/ijt/ijt990302.htm>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res*. 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarrre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res*. 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J*. 1959 Dec 26; 2 (5164): 1448-52. PMID: 14436154.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):Trans-sexualism and Sex reassignment. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res*. 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav*. 1999 Feb;28(1):71-89. PMID: 10097806.

Reisner S, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, Holland C, Max R, Baral S. Global health burden and needs of transgender populations: a review. *Lancet*. Epub 16 June 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)00684-X](http://dx.doi.org/10.1016/S0140-6736(16)00684-X)

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand*. 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav*. 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl*. 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav*. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health*. 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract*. 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18 (88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193-236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carter RA. New Women: Sexological outcomes of male-to-female gender reassignment surgery. *JSET*. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg*. 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol*. 2011 May;8 (5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol*. 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer*. 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law*. 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology*. 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT*. 2001 Jul-Sept; 5(3):20 pages.http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev*. 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract*. 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract*. 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001 Apr;40(4):472-81. PMID: 11314574.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res*. 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand*. 1981 May;63 (5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand*. 1981 Jul;64 (1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav* 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):192-206Epub 2010 Mar 29. PMID: 20347346.

Steinle K. Hormonal management of the female-to-male transgender patient. *J Midwifery Womens Health*. 2011 May-Jun;56(3):293-302. PMID: 21535376.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav*. 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J*. 1972 Mar;68 (3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat*. 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBek), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev*. 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills*. 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2004 Dec;19(6):301-12. PMID: 15724806.

Swaab DF, Garcia-Falgueras A. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Funct Neurol*. 2009 Jan-Mar;24(1):17-28. PMID: 19403051.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res*. 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res*. 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female- to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand*. 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman J. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom*. 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry*. 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand*. 1988 Oct;78 (4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J*. 1992 Apr;33(2):162-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J*. 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore*. 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess*. 1979. Aug;43(4):385-7. PMID: 383946.

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007 Oct;83(984):638-42. PMID: 17916872.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol*. 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol*. 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedeker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab*. 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsson T, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierzak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med*. 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. *Arch Sex Behav*. 2015 Jul;44 (5):1281-7. Epub 2015 Jan 15. PMID: 25588709.

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav*. 2013; 42:361-70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav*. 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med*. 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mrvošević Marojević L, Ivović M, Tančić-Gajić M, Stojanović M, Marina LV, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal*. 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow-up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry*. 1978;132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. *Lancet*. Epub 16 June 2016 [http://dx.doi.org/10.1016/S0140-6736\(16\)00683-8](http://dx.doi.org/10.1016/S0140-6736(16)00683-8)

Weigert R, Frison E, Sessieq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology*. 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quality of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people. Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV*. World Health Organization. July 2015. <http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/>.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*. 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van de Peer F, Dedeker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

Wylie K, Knudson G, Khan S, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet*. Epub 16 June 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)00682-6](http://dx.doi.org/10.1016/S0140-6736(16)00682-6)

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedeker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med*. 2012 Oct;9(10):2641- 51. Epub 2012 Aug 20. PMID: 22906135.

C-Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav*. 2012 Oct;41(5):1069-71. PMID: 22968492.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction.* 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health.* 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex.* 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S. The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract.* 1999; 49 (449): 991-2. PMID: 10824346.

Wilson RC, Nimkarn S, Domic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic- specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21- hydroxylase deficiency. *Mol Genet Metab.* 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab.* 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect.* 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol.* 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav*. 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol*. 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav*. 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders*. (6th version) February, 2001.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr*. 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez- Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab*. 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals*. (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5 α -Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopoulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg*. 2006 May;77(5):432-8. German. Erratum in *Chirurg*. 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis*. 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry*. 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res*. 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901-14. PMID: 23868018.

EXHIBIT G

Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

[Back to Top](#)

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Final Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: August 30, 2016

I. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
 AIDS - Acquired Immune Deficiency Syndrome
 ANOVA - Analysis of Variance
 APA - American Psychiatric Association
 APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
 BIQ - Body Image Questionnaire
 BSRI - Bem Sex Role Inventory
 CCEI - Crown Craps Experimental Index
 CDC - Centers for Disease Control
 CHIS - California Health Interview Survey
 CI - Confidence Interval
 CMS - Centers for Medicare & Medicaid Services
 DAB - Departmental Appeals Board
 DSM - Diagnostic and Statistical Manual of Mental Disorders
 EMBASE - Excerpta Medica dataBASE
 FBeK - Fragebogen zur Beurteilung des eigenen Körpers
 FDA - Food and Drug Administration
 FPI-R - Freiburg Personality Inventory
 FSFI - Female Sexual Function Index
 GAF - Global Assessment of Functioning
 GID - Gender Identity Disorder
 GIS - Gender Identity Trait Scale
 GRS - Gender Reassignment Surgery
 GSI - Global Severity Indices
 HADS - Hospital Anxiety Depression Scale
 HHS - U.S. Department of Health and Human Services
 HIV - Human Immunodeficiency Virus
 IIP - Inventory of Interpersonal Problems
 IOM - Institute of Medicine
 KHQ - King's Health Questionnaire
 LGB - Lesbian, Gay, and Bisexual
 LGBT - Lesbian, Gay, Bisexual, and Transgender
 MAC - Medicare Administrative Contractor
 MMPI - Minnesota Multiphasic Personality Inventory
 NCA - National Coverage Analysis
 NCD - National Coverage Determination
 NICE - National Institute for Health Care Excellence
 NIH - National Institutes of Health
 NZHTA - New Zealand Health Technology Assessment
 PIT - Psychological Integration of Trans-sexuals
 QOL - Quality of Life
 S.D. - Standard Deviation
 SADS - Social Anxiety Depression Scale
 SCL-90R - Symptom Check List 90-Revised
 SDPE - Scale for Depersonalization Experiences
 SES - Self Esteem Scale

SF - Short Form

SMR - Standardized Mortality Ratio SOC – Standards of Care

STAI-X1 - Spielberger State and Trait Anxiety Questionnaire

STAI-X2 - Spielberger State and Trait Anxiety Questionnaire

TSCS - Tennessee Self-Concept Scale

U.S. - United States

VAS - Visual Analog Scale

WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100

WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Although there are other therapeutic options for gender dysphoria, consistent with the NCA request, this decision only focuses on gender reassignment surgery.

B. Prevalence of Transgender Individuals

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

Most recently, the Williams Institute published a report that utilized data from the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS). Overall, they found that 0.6% or 1.4 million U.S. adults identify as transgender. The report further estimated 0.7% of adults between the ages of 18-25 identify as transgender, 0.6% of adults between the ages of 25-65 identify as transgender, and 0.5% of adults age 65 or older identify as transgender (Flores et al., 2016).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. (CMS Office of Minority Health 2015).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson and Moller 2003).

III. History of Medicare Coverage

Date	Action
August 1, 1989	CMS published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.

CMS does not currently have a NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a NCA for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A) Under §1832 (Scope of Part B)
 Under §1861(s) (Definition of Medical and Other Health Services)
 Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
December 3, 2015	CMS accepts an external request to open a NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.
June 2, 2016	Proposed Decision Memorandum posted on the web site and the final 30 day public comment period commenced.
July 2, 2016	Final comment period closed. CMS received 45 comments.

V. FDA Status

Surgical procedures per se are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved and/or cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer-reviewed medical journals. We also considered articles cited by the requestor, articles identified in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies for gender dysphoria. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) and/or quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), suicide (attempts), mortality, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). Reliability and validity are important because when evaluating patients with gender dysphoria most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded. The CMS initial internal search for the proposed decision memorandum was limited to articles published prior to March 21, 2016. The CMS internal search for the final decision memorandum continued through articles published prior to July 22, 2016.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early

termination, completed, ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. For this final decision, CMS also reviewed all evidence submitted via public comment.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this specific NCA, CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as one study (Udeze et al., 2008; Megeri and Khoosal, 2007). A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study. The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

Figure 1 Legend: The studies in Figure 1 are categorized into three groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only population box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of patients whose treatment could involve a variety of therapeutic interventions, but who were not stratified by that treatment.

When looking at the totality of studies, the 33 studies could be characterized by the following research design groups:

a. Observational, mixed population of surgical and non-surgical patients without stratification

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635-42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design to assess a mixed population treated with hormones, as well as, reassignment surgery in comparison to a population-based cohort. The study was not designed to assess the specific impact of gender reassignment surgery on clinical outcomes.

The investigators assessed mortality in patients who (a) were from a single-center, unspecified, Dutch university specialty clinic, (b) had initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed (with or without continued hormone treatment) by the clinic for at least one year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population were obtained through the Central Bureau of Statistics of the Netherlands (Centraal Bureau voor de Statistiek). Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male-to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio difference 1:2.4 with a p-value $p < 0.0001$). Later calculations did not distinguish between those with hormone therapy alone versus those with hormone therapy plus reassignment surgery. The mean age at the time of hormone initiation in female-to-male and male-to-female patients was 26.1 ± 7.6 (range 16–56) years and 31.4 ± 11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p < 0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8 ± 6.3 and 19.4 ± 7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy with or without surgical reassignment. Of these patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality for this mixed population was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI] 1.47–1.55) for males-to-females when compared to males in the general Dutch population. The increase in all-cause mortality (12%) for females-to-males when compared to females in the general Dutch population was not statistically significant (95% CI 0.87–1.42).

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients but only in older patients ($n=18$, SMR 1.64 [95% CI 1.43–1.87]), mean age [range]: 59.7 [42–79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28–7.63], $p=0.01$). There was a small, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Other contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide ($n=17$, SMR 5.70 [95% CI 4.93–6.54]), AIDS ($n=16$, SMR 30.20 [95% CI 26.0–34.7]), and illicit drug use ($n=5$, SMR 13.20 [95% CI 9.70–17.6]). An additional major contributor was “unknown cause” ($n=21$, SMR 4.00 [95% CI 3.52–4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and six (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Overall mortality, and specifically breast cancer and cardiovascular disease, were not increased in the hormone-treated female-to-male patients. Asscheman et al. reported an elevated SMR for illicit drug use ($n=1$, SMR 25

Printed on 11/17/2016. Page 11 of 150

This study subsumes earlier publications on mortality (Asscheman et al. 1989 [n=425]; Van Kesteren et al. 1997 [n=816]).

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone- treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1 ± 8.0 . HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87 ± 9.15 years (range 15-61). The current age of patients using hormones was 33.6 ± 9.1 years (n=120) and older than the age of patients without hormone treatment (25.9 ± 7.5) ($p=0.001$). The age at hormone initiation, however, was 24.6 ± 8.1 years.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female (ratio 1:1.7). The number of patients not on hormones and who had undergone at least one gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, and/or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and/or vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was 9 in transsexuals without hormone treatment and 6.4 in transsexuals with hormone

treatment. The mean scores for HAD-Anxiety, HAD-Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery undergoing various stages of treatment.

The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center (Barcelona, Spain), specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but not genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty). The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL- BREF) was used to evaluate quality of life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

All consecutive patients presenting at the clinic (277) were recruited and, 260 (93.9%) agreed to participate. Of this number, 59 of these were excluded for incomplete questionnaires, 8 were excluded for prior genital reassignment surgery, and 193 were included in the study (the mean age of this group was 31.2 ± 9.9 years (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients (ratio 1:1.6). Of these, 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy $n=19$ (25.7%); mastectomy $n=29$ (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least one non-genital surgical procedure with mammoplasty augmentation being the most common procedure, $n=47$ (39.5%), followed by facial feminization, $n=11$ (9.2%), buttocks feminization, $n=9$ (7.6%), and vocal feminization (thyroid chondroplasty), $n=2$ (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81 ± 14.89 (range 12.50-96.88), "Physical" 63.51 ± 17.79 (range 14.29-100), "Psychological" 56.09 ± 16.27 (range 16.67- 56.09), "Social" 60.35 ± 21.88 (range 8.33-100), and "Global QOL and Health" 55.44 ± 27.18 (range 0-100 with higher score representing better QOL). The mean APGAR family score was 7.23 ± 2.86 (range 0-10 with a score of 7 or greater indicative of family functionality).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all four domains and

the general health and quality of life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a single-site (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2 ± 10.3 years. Of the participants, seven had undergone reassignment surgery, 10 pre-surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

HADS scores were missing for at least one person. The HADS test revealed non-pathologic results for depression (female-to-male: 6.64 ± 5.03 ; male-to-female: 6.58 ± 4.21) and borderline results for anxiety (female-to-male: 7.09 ± 5.11 ; male-to-female: 7.74 ± 6.13 , where a result of 7-10 = possible disorder). There were no differences by natal gender. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted a two center (Lund and Umeå, Sweden) non-blinded, observational study using a

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥ 1 year of real-life experience in preferred gender, and ≥ 1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment five or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) two or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a three or five point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre-specified except for GAF, which pre-specified a difference to mean change ≥ 5 points. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, 42 (70.0% of eligible) (17 [40.5 %] female-to-male; 25 [59.5%] male-to-female; ratio 1:1.5) were available for follow-up. Of these, 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including one post mastectomy), five were still in the process of completing surgery, and five (one female-to-male; four male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The age (ranges) of the patients at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22- 49), and 38.9 (28-53) years in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) years in the male- to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p < 0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improved in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to- female patients. A ≥ 5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these 42 patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery ($n=32$) and mastectomy only ($n=one$), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38.1%) (41.2% of female- to-male; 36.0% of male-to-female patients) were reported to have a partner. Yet more than that number commented on partner relationships: (a) 62.2 % of the 37 who answered (50.0% of female- to- male; 69.6% of male-to-female patients) reported improved partner relationships (five [11.9%] declined to answer.); (b) 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female patients) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification. In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers.

This study subsumes earlier work by Bodlund et al. (1994, 1996). The nationwide mortality studies by Dhejne et al. (2011) may include all or part of this patient population.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a single-center (Albany, New York) a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p < 0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; Of the patient population, 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to- male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to-female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality of life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single Belgian university specialty clinic at Ghent. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 years (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metaoidplasty eight (with five of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation three.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality of life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metaoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality of life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res.* 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross-sectional design and a non-specific quality of life tool in a mixed population with and without hormone therapy and/or reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the Short-Form 36 (SF-36) Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the eight domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males-or-females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6 ± 10.8 years. Of these 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. Of these, 254 (67.0%) reported prior or current testosterone use while 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery.

Complete SF-36 data were available for 376 U.S. respondents. For the complete, non-stratified U.S. cohort the Physical Summary Score (53.45 ± 9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was within one standard deviation of the normative mean. The Mental Summary Score (39.63 ± 12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50 ± 10) ($p < 0.001$), but was well within two standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12 ± 10.2), Role Emotional (42.42 ± 11.6), Social Functioning (43.14 ± 10.9), and Vitality (46.22 ± 9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within one standard deviation of the normative sub-score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22 ± 11.9) than those with "No Testosterone Usage" (36.08 ± 12.6) ($p=0.001$). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21 ± 11.6) and those without "Top Surgery" (38.01 ± 12.5) ($p=0.067$). These differences were well within one standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

b. Observational, surgical series, without concurrent controls

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun; 53(3):295-304.

Blanchard et al. conducted a single-center (Ontario, Canada), prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non-specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least one year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using Blanchard's Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R). Differences in test scores considered to be biologically significant were not pre-specified in the methods.

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 263 were diagnosed with gender dysphoria. Of these 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically ($p=0.01$).

Additional surgical procedures in female-to-male patients included: oophorectomy/hysterectomy (92.1%) and phalloplasty (7.9%). Additional surgical procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation (53.1%). Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis (100%) and breast implantation (33.3%). The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all three patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 65.2% of female-to-male patients cohabitated with partners of their natal gender; 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; and no male-to-female patients with female partner preference cohabitated with partners of their natal gender.

Of participants, 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (one female-to-male; one male-to-female with male partner preference; three male-to-female with female partner preference) indicated that they probably would undertake the surgery again. Post hoc analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with an investigator designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery.

Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; eight (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their sexual orientation; 13 (26%) declined to answer the question. The study found that two female-to- male patients and two male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

Hess et al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed anonymous questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic (Essen, Germany). Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44 ± 9 (range 18-70) years and mean duration after surgery was 3 ± 1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality of life was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed in the more distant past; whereas, more satisfaction with vaginal depth and width was present in more recent surgical treatment.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun; 66(4):371-2. PMID: 22624747.

Salvador et al. conducted a single center (Port Alegre, Brazil) prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 82 underwent sex reassignment surgery. There were 69 participants with a minimum 2-year follow up, of whom 52 patients agreed to participate in the study. The age at follow-up was 36.3 ± 8.9 (range 15-58) years with the time to follow-up being 3.8 ± 1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J*. 1993 Dec; 34(6):515-7.

Tsoi conducted a single-center (Singapore) prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigator assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥ 6 months, and willingness to function in the life of the desired gender for ≥ 6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 (44.4%) were female-to-male and 45 (55.6%) were male-to-female (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4 ± 4.4 (range 14-36) and 27.4 ± 4.0 ; (range 14-36); male-to-female 22.9 ± 4.6 (range 14-36) and 24.7 ± 4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender

reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p < 0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

Weyers et al. (2009) conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with two self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior four weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center (Ghent, Belgium), specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed seven question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 (71.5% of the eligible recruits) participants. Analysis of the data revealed that the patient's average age was 43.1 ± 10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95 ± 10.04 out of a maximal 50. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46 ± 1.57 , desire 3.12 ± 1.47 , arousal 2.95 ± 2.17 , lubrication 2.39 ± 2.29 , orgasm 2.82 ± 2.29 , and pain 2.21 ± 2.46 . Though these numbers were reported in the study, data on test population controls were not provided.

A post hoc exploration of the data suggested the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med. 2011 Dec;8 (12):3379-88. Epub 2011 Jun 23.

Wierckx et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with three self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic (Ghent, Belgium). Investigators used the Dutch version of the SF-36 with 36 questions, eight subscales, and two domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self-designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were recruited; ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the one year window. The age of patients was: 30 ± 8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ± 8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oophorectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metoidioplasty ($n=9$; 18.4%), phalloplasty ($n=8$ after metoidioplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device ($n=32$; 65.3%). All had started hormonal therapy at least two years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1 ± 20.7 versus 71.9 ± 18.3 and 72.6 ± 19.2 versus 79.3 ± 16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

c. Observational, surgical patients, cross-sectional, with controls

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery.

The mean age for each of these cohorts was: 50 years (no standard deviation [S.D.]) only reassignment surgery, 51 years (no S.D.) only facial surgery, 49 years (no S.D.) both types of surgery, and 46 years (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than one year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within one standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within one standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a single center (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post- surgical cohorts. Patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Körpers (FBek) which contained three domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0 ± 11.3 years; post-operative 38.2 ± 9.0 years. The mean duration after reassignment surgery was 51 ± 25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0 ± 3.8 versus 5.1 ± 3.7 ; male-to-female 8.1 ± 4.5 versus 4.7 ± 3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1 ± 2.9 versus 8.9 ± 3.1 ; male-to-female 7.0 ± 2.9 vs 9.5 ± 2.6 .

Mate-Kole et al. conducted a single site (London, United Kingdom) prospective non-blinded, observational study using a cross-sectional design and two psychological tests (one with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients from Charing Cross Hospital. The mean ages of the three cohorts were as follows: 34 years for patients undergoing evaluation; 35 years for wait-listed patients; and 37 years for post-operative patients. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, while 14% in each cohort, respectively, had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were statistically higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were statistically lower in the post-operative cohort than in the other two cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The Bem Sex Role Inventory femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy non-transgender volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation.

The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to-female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 years (range 29- 67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinic (Bern, Switzerland), and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality of life assessment tools included a VAS and the King's Health Questionnaire (KHQ), which consists of eight domains with scores between zero and five or one and five, with lower scores indicating higher preference. The KHQ and the numerical change/difference required for clinical significance (≥ 5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex. No corroborative gynecologic or urologic evaluations were undertaken.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of this study was 51 years (range 39-62 years). The patients had undergone a median of nine surgical procedures in comparison to the two undergone by controls. Reassignment patients were less likely to be married (23.6% versus 65%; $p=0.002$); partnership status was unknown in five patients. The scores of VAS global satisfaction (maximal score eight) were lower for surgically reassigned patients (4.49 ± 0.1 SEM) than controls (7.35 ± 0.26 SEM) ($p<0.0001$).

The abstract stated that quality of life was lower in reassignment patients 15 years after surgery relative to controls. One table in the study, Table 2, delineated statistically and biologically significant differences for four of the eight KHQ domains between the patients and controls: physical limitation: 37.6 ± 2.3 versus 20.9 ± 1.9 ($p<0.0001$), personal limitation: 20.9 ± 1.9 versus 11.6 ± 0.4 ($p<0.001$), role limitation: 27.8 ± 2.4 versus 34.6 ± 1.7 ($p=0.046$), and general health: 31.7 ± 2.2 versus 41.0 ± 2.3 ($p<0.02$). There is a related paper by Kuhn

Printed on 11/17/2016. Page 28 of 150

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a single-center (Oslo, Norway) partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by two senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre- surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post-surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34 ± 9.5 years and female-to-male 33.3 ± 10.0 years. The other control group consisted of patients with personality disorder. Of these, 101 (27 men (33.9 ± 7.3 years) and 74 women (31.6 ± 8.2)) were tested during a treatment program. One year later, 98% were evaluated. A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post-reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7 ± 1 . The Global Assessment of Function was higher (better) in the gender dysphoric groups (78.0 ± 8.9) than in the personality disorder cohort (53.0 ± 9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67 ± 0.57 and 0.56 ± 0.45 . Although they were nominally higher than the healthy normative controls (males: 0.32 ± 0.36 and females 0.41 ± 0.43), they were well within the non- pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without GRS), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50 ± 10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

d. Observational, surgical patients, longitudinal, with controls

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One.* 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed conditions such as, but not limited to, mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were the 2002 WPATH criteria and included evaluation and treatment by one of six specialized teams, name change, a new national identity number indicative of gender, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided.

Investigators identified 804 patients with gender identity disorder (or some other disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3 ± 8.7 (range 20–62) and 36.3 ± 10.1 (range 21–69) years, respectively. Immigrant status was two times higher in reassigned patients ($n=70$, 21.6%) than in either type of control (birth [natal] sex matched $n=294$ [9.1%] or reassigned gender matched $n=264$ [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients ($n=151$ [57.8%]) than in either type of control (birth sex matched $n=1,725$ [61.5%] or reassigned gender matched $n=1804$ [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients ($n=58$, 17.9%) than in either type of control (birth sex matched $n=123$ [3.8%] or reassigned gender matched $n=114$ [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery ($n=27$ [8.3%]) than in controls (hazard ratio 2.8 [CI 1.8–4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. Survival rates at 20 year follow-up (as derived from figure 1) were: female control 97%, male controls 94%, female-to-male patients 88%, and male-to-female patients 82%. The major contributor to this mortality difference was completed suicide ($n=10$ [3.1%]; adjusted hazard ratio 19.1 [CI 5.8–62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients ($n=9$ [2.8%]) than in controls (hazard ratio 2.5 [CI 1.2–5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery ($n=29$ [9.0%]) than in controls (adjusted hazard ratio 4.9 [CI 2.9–8.5]). Male-to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons $n=64$ [20.0%] than in controls (hazard ratio 2.8 [CI 2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landén et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with "regret" in a national database. This same group (Landén et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra- group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least one year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After two years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures (Dhejne et al., 2011). Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real- life experience phase, and family support.

There were 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6). The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.8% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female-to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. This number appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense (usually in Thailand or the U.S.). This cohort (6% of 681) includes one person who was denied reassignment surgery by Sweden.

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting the diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex- reassignment surgery outside of Sweden (36 of these 41 had surgery after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male (n=5): male-to-female (n=10) ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger at the time of initial surgical application (median age 22 years) than the complete female-to-male cohort at the time of surgical application (median age 27 years). By contrast the male-to-female applicants for reversal were older at the time of initial surgical application (median age 35 years) than the complete male-to-female cohort at the time of initial surgical application (median age 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landén et al. extracted data from medical records and government verdicts. Pearson Chi-square testing with Yates' correction for small sample sizes was used to identify candidate variables predictive of regret. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. Univariate regression analyses further clarified the most important variables. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional multivariate regression analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables had a more than additive effect.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and most of the Dhejne (2014) population. There is a related paper by Landén et al. 1998b that included the criteria to qualify for surgical intervention at that time.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with eight subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty-six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% for the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3 ± 32.4 . The respective scores for the various gender dysphoric cohorts were 157.7 ± 49.8 at initial presentation, 119.7 ± 32.1 after hormone therapy, and 127.9 ± 37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Kockott and Fahrner conducted a single center (Munich, Germany) prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument developed according to the scale used by Hunt and Hampson (1980) for assessment of 17 post-operative patients. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5 ± 13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7 ± 10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3 ± 9.4 years. The age of the patients who were no longer interested in surgery was 31.8 ± 6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between "few difficulties" (10-18) and "distinct difficulties" (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score within each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences between groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having "distinct difficulties" in
Printed on 11/17/2016. Page 35 of 150

psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a single-center (Baltimore, Maryland, U.S.) prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least one year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive two to four hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score. The score value or the change score that was considered to be biologically significant was not pre-specified in the methods.

The clinic opened with 100 patients, but when the follow-up was completed, 52 patients were interviewed and 50 gave consent for publication. Of these, 15 (four female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (one female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (five female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 33% had some type of psychiatric contact prior to the initial clinic evaluation and 8% had psychiatric contact during the follow-up. Of the patients who had not undergone surgery or who had done so later, 72% had some type of psychiatric contact prior to the initial clinic evaluation and 28% had psychiatric contact during follow-up. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. The absolute score value at follow-up was the same for both groups (1.07+1.53 and 1.10+1.97 respectively). By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere. The absolute score value at follow-up was 0.21+1.89.

Related papers include Meyer et al. (1971), Meyer et al. (1974a-d), and Derogatis et al. (1978) along with commentary response by Fleming et al. (1980).

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. single-center (Belgrade, Yugoslavia) conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator- designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least six months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least one year and sexual orientation to non-natal sex. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 34 were eligible for the study and 32 participated in the study (two were lost to follow-up and four were in the peri-operative period) - 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ± 13.4 months (range 6 months to 4 years). The age was female-to-male 27.8 ± 5.2 (range 23-37) and male-to-female 26.4 ± 7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and eight (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Rupp and Pfafflin conducted a single-center (Ulm, Germany) partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results. Changes or inter-group differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included.

Overall, 140 patients received recruitment letters and then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2 ± 5.78 years (female-to-male) and 52.9 ± 10.82 years (male-to-female). The intervals for follow-up were 14.1 ± 1.97 years and 13.7 ± 2.17 years, respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oophorectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty. Of male-to-female patients, 94.3% had undergone vaginoplasty and perhaps an additional procedure (breast augmentation, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35 ± 0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not being in a steady relationship. Regular sexual relationships were reported by 57.1% of 35 female- to-male respondents and 39.4% of 33 male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. The effect size was statistically significant and large only for the "Interpersonal Sensitivity" scale (one of 10 parameters). The absolute magnitude of mean change was small: from 0.70 ± 0.67 to 0.26 ± 0.34 (scale range 0-4). The duration of follow-up did not correlate with the magnitude of change on the various scales. Differences in baseline SCL-90R scores of 62 participants were compared with the score of 63 of the 69 eligible recruits who declined to enter the study and were notable for higher "Depression" scores for the latter.

Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. The effect size was statistically significant and large only for the "Overly Accommodating" scale (one of eight parameters). The absolute magnitude of mean change was small: from 11.64 ± 5.99 to 7.04 ± 4.73 (scale range 0-32). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was statistically significant and large only for the "Life Satisfaction" scale (one of 12 parameters). The absolute magnitude of mean change was substantive: from 4.43 ± 2.99 to 8.31 ± 2.63 (scale range 0-12). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female to male patients and 19 of 35 male to female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

This current report is an update of prior publications by Pfafflin including work with Junge which was published in a variety of formats and initially in German.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a single-center (Amsterdam, Netherlands) prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigators assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post- surgery data were acquired at least one year post reassignment surgery.

Three hundred twenty five consecutive adolescents and adults were screened for the study. One-hundred three (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy.

Subsequently, the study analysis was limited to adults. One hundred sixty-two (58 [38.9%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing and remained in the normal range after surgery. SCL global scores for psycho- neuroticism were minimally elevated before surgery 143.0 ± 40.7 (scoring range 90 to 450) and normalized after surgery 120.3 ± 31.4 . (An analysis using patient level data for only the completers was not conducted.)

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to- female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed) and Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed)

Udeze et al. conducted a single-center (Leicester, United Kingdom) prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within six months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33 ± 13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

e. Randomized, surgical patients, longitudinal, with controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole et al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic (London, United Kingdom). Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥ 2 year desire to change gender, a ≥ 1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at six months for diagnostic confirmation and exclusion of psychosis.

Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator-designed survey with questions about social life and sexual activity.

The mean age and range of the entire cohort was 32.5 years (21-53). Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms (Birchnell et al. 1988). Over the two year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic range for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior two years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the two cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities.

2. External Technology Assessments

- a. CMS did not request an external technology assessment (TA) on this issue.
- b. There were no AHRQ reviews on this topic.
- c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

There were two publications in the COCHRANE database, and both were tangentially related. Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.
Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations
Boehmer U. *Am J Public Health*. 2002; 92: 1125–30.

“Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking.”

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

“Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed.”

- e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. NZHTA Report. February 2002;1(1). http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following:

1. Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists?

2. If there is evidence of effectiveness, what subgroups would benefit from GRS?"

The authors concluded that there was not enough evidence to answer either of the research questions.

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document: Health Care for Transgender Individuals: Committee Opinion
Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gynecol. 2011;118:1454-8.

"Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. Arch Sex Behav. 2012; 41:759-96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RCTs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial.”

[G] Other. Opinion-like essays, case reports, and other reports not categorized above.”

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. J Clin Endocrinol Metab. 2009; 94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

“This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low.”

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K. www.wpath.org/_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf *Int J Transgend.* 2011;13:165–232.

The WPATH is “an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health.”

WPATH reported, “The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person’s gender identity and that person’s sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).”

The WPATH standards of care (SOC) “acknowledge the role of making informed choices and the value of harm-reduction approaches.”

The SOC noted, “For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.”

e. American Psychological Association

Suggested citation until formally published in the American Psychologist: American Psychological Association. (2015): *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People Adopted by the Council of Representatives, August 5 & 7, 2015*. www.apa.org/practice/guidelines/transgender.pdf

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. <http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx>

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and

monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination.”

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013.
http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LGBT research Coordinating Committee noted that most of the health research for this set of populations is “focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism.”

6. Pending Clinical Trials

ClinicalTrials.gov

There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies either took place in or a suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as “clients” instead of “patients,” and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire).

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS’ experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: <https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n#Results>

a. Initial Comment Period: December 3, 2015 – January 2, 2016

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups.

b. Second Comment Period: June 2, 2016 – July 2, 2016

During the second 30-day public comment period, we received a total of 45 public comments, 7 of which were not posted on the web due to personal health information content. Overall, 82% supported coverage of gender reassignment surgery, 11% opposed, and 7% were neutral or silent in their comment whether they supported or opposed coverage. Half of the comments were submitted by individuals who expressed support for coverage of gender reassignment surgery (51%). We also received comments from physicians, providers, and other health professionals who specialize in healthcare for transgender individuals (17%). We received one comment from a municipality, the San Francisco Department of Public Health. Associations (American Medical Association, American College of Physicians, American Academy of Nursing, American Psychological Association, and LGBT PA Caucus) and advocates (Center for American Progress with many other signatories, Jamison Green & Associates) also submitted comments.

Below is a summary of the comments CMS received. In some instances, commenters identified typographical errors, context missed, and opportunities for CMS to clarify wording and classify articles for ease of reading in the memorandum. As noted earlier, when appropriate and to the extent possible, we updated the decision memorandum to reflect those corrections, improved the context, and clarified the language. In light of public comments, we re-evaluated the evidence and our summaries. We updated our summaries of the studies and clarified the language when appropriate.

1. Contractor Discretion and National Coverage Determination

Comment: Some commenters, including advocates, associations, and providers, supported CMS' decision for MAC contractor discretion/case-by-case determination for gender reassignment surgery. One stakeholder stated, "We agree with the conclusion that a NCD is not warranted at this time."

Response: We appreciate the support and understanding among stakeholders for our proposed decision to have the MACs determine coverage on a case-by-case basis. We have clarified in this final decision memorandum that

coverage is available for gender reassignment surgery when determined reasonable and necessary and not otherwise excluded by any other relevant statutory requirements by the MAC on a case-by-case basis. "The case-by-case model affords more flexibility to consider a particular individual's medical condition than is possible when the agency establishes a generally applicable rule." (78 Fed. Reg. 48165 (August 7, 2013)).

Comment: Some commenters cautioned that CMS' choice to not issue a NCD at this time must not be interpreted as a national non-coverage determination or used in any way to inappropriately restrict access to coverage for transgender Medicare beneficiaries or other transgender individuals. Multiple commenters indicated their disappointment that CMS did not propose a National Coverage Determination (NCD) and, instead, chose to continue to have local MACs make the coverage decisions on a case-by-case basis. Commenters stated this could result in variability in coverage.

Response: We appreciate the comments. We are not issuing a NCD at this time because the available evidence for gender reassignment surgery provides limited data on specific health outcomes and the characteristics of specific patient populations that might benefit from surgery. In the absence of a NCD, the MAC's use the same statutory authority as NCDs, section 1862(a)(1)(A) of the Social Security Act (the Act). Under section 1862(a)(1)(A) an item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. While CMS did not have enough evidence to issue a NCD, we believe the MACs will be able to make appropriate coverage decisions on a case-by-case basis taking into account individual characteristics of the Medicare beneficiary.

Comment: Some commenters sought a NCD that would establish guidelines for coverage and include elements such as a prescribed set of surgeries and a shared decision making element.

Response: For the reasons stated above, we are not issuing a NCD at this time and, therefore, are not establishing specific gender reassignment surgery coverage guidelines for the Medicare program. We generally agree that shared decision-making is a fundamental approach to patient-centered health care decisions and strongly encourage providers to use these types of evidence based decision aids. We have not found a shared decision aid on GRS and encourage the development of this necessary element to conduct formal shared-decision making.

Comment: Some commenters expressed concern that there is a misunderstanding of transgender individuals as having a disorder or being abnormal. Some commenters indicated a history of bias and discrimination within society as a whole that has occurred when transgender individuals have sought health care services from the medical community. Some commenters are concerned that the decision not to make a NCD will subject individuals seeking these services to corporate bias by Medicare contractors.

Response: We acknowledge the public comments and that there has been a transformation in the treatment of individuals with gender dysphoria over time. In this NCA, we acknowledge that gender dysphoria is a recognized Diagnostic and Statistical Manual of Mental Disorders (DSM) condition. With respect to the concern about potential bias by Medicare contractors, we have no reason to expect that the judgments made on specific claims will be influenced by an overriding bias, hostility to patients with gender dysphoria, or discrimination. Moreover, the Medicare statute and our regulations provide a mechanism to appeal an adverse initial decision if a claim is denied and those rights may include the opportunity for judicial review. We believe the Medicare appeals process would provide an opportunity to correct any adverse decision that was perceived to have been influenced by bias.

Comment: Commenters mentioned the cost of gender reassignment surgery could influence MAC decision making.

Response: The decisions on whether to cover gender reassignment surgery in a particular case are made on the basis of the statutory language in section 1862 of the Social Security Act that establish exclusions from coverage and would not depend on the cost of the procedure.

2. Coverage with Evidence Development and Research

Comment: In our proposed decision memorandum, we specifically invited comments on whether a study could be developed that would support coverage with evidence development (CED). One organization commented, "We strongly caution against instituting a CED protocol." Commenters were opposed to coverage limited in clinical trials, suggesting that such coverage would restrict access to care. Several commenters provided suggested topics for clinical research studies for the transgender population. For example, one commenter suggested a study of non-surgical treatment for transgender children prior to puberty.

Response: While we appreciate the comments supporting further research, in general, for gender reassignment surgery, we agree that CED is not the appropriate coverage pathway at this time. While CED is an important mechanism to support research and has the potential to be used to help address gaps in the current evidence, we are not aware of any available, appropriate studies, ongoing or in development, on gender reassignment surgery for individuals with gender dysphoria that could be used to support a CED decision.

3. Gender Reassignment Surgery as Treatment

Comment: One group of commenters requested that CMS consider that, “The established medical consensus is that GRS is a safe, effective, and medically necessary treatment for many individuals with gender dysphoria, and for some individuals with severe dysphoria, it is the only effective treatment.”

Response: We acknowledge that GRS may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a NCD that identifies the precise patient population for whom the service would be reasonable and necessary.

4. Physician Recommendations

Comment: Several commenters stated that gender reassignment surgery should be covered as long as it was determined to be necessary, or medically necessary by a beneficiary’s physician.

Response: Physician recommendation is one of many potential factors that the local MAC may consider when determining whether the documentation is sufficient to pay a claim.

5. WPATH Standards of Care

Comment: Several commenters suggested that CMS should recommend the WPATH Standards of Care (WPATH) as the controlling guideline for gender reassignment surgery. They asserted it could satisfy Medicare’s reasonable and necessary criteria for determining coverage on a case-by-case basis.

Response: Based on our review of the evidence and conversations with the experts and patient advocates, we are aware some providers consult the WPATH Standards of Care, while others have created their own criteria and requirements for surgery, which they think best suit the needs of their patients. As such, and given that WPATH acknowledges the guidelines should be flexible, we are not in the position to endorse exclusive use of WPATH for coverage. The MACs, Medicare Advantage plans, and Medicare providers can use clinical guidelines they determine useful to inform their determination of whether an item or service is reasonable and necessary. When making this determination, local MACs may take into account physician’s recommendations, the individual’s clinical characteristics, and available clinical evidence relevant to that individual.

6. Scope of the NCA Request

Comment: One commenter stated that CMS did not address the full scope of the NCA request.

Response: The formal request for a NCD is publicly available on our tracking sheet. (<https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id282.pdf>) The letter did not explicitly seek a national coverage determination related to counseling or hormone therapies, but focused on surgical remedies. CMS is aware that beneficiaries with gender dysphoria use a variety of therapies.

Comment: Other commenters stated the scope of the proposed decision is unnecessarily broad because it discussed therapies other than surgery. They suggested this discussion could lead to the unintended consequence of restricting access to those services for transgender Medicare beneficiaries and other transgender individuals.

Response: As we noted in our proposed decision, our decision focused only on gender reassignment surgery. In the course of reviewing studies related to those surgeries, occasionally authors discussed other therapies that were mentioned in our summaries of the evidence. To the extent possible, we have modified our decision to eliminate the discussion of other therapies which were not fully evaluated in this NCA.

7. NCA Question

Comment: Some commenters expressed concern about the phrasing of the question in this NCA.

Response: The phrasing of the research question is consistent with most NCAs and we believe it is appropriate.

8. Evidence Summary and Analysis

Comment: Several commenters disagreed with our summary of the clinical evidence and analysis. A few commenters contended that the overall tone of the review was not neutral and seemed biased or flawed. One commenter noted that the Barrett publication was available on the Internet.

Response: We appreciate the comments that identified technical errors, and we made the necessary revisions to this document. However, we disagree with the contention that our evidence review was not neutral and seemed biased or flawed. We believe that the summary and analysis of the clinical evidence are objective. As with previous NCAs, our review of the evidence was rigorous and methodical. Additionally, we reviewed the Barrett publication, but it did not meet our inclusion criteria to be included in the Evidence section.

9. Evidence Review with Transgender Experts

Comment: Several commenters requested that CMS re-review the clinical evidence discussed in the proposed decision memorandum with outside experts in the field of transgender health and transition/gender reassignment-related surgeries. Several offered the expertise within their organization to assist in this effort.

Response: We appreciate these comments and the transgender health community's willingness to participate. For this NCA we discussed gender reassignment surgery protocols with experts, primarily in coordinated care settings. Additionally, the public comment periods provide opportunities for expert stakeholder input. According to our process for all NCAs, we do not jointly review evidence with external stakeholders but have carefully reviewed the very detailed comments submitted by a number of outside experts in transgender health care.

10. Previous Non-Coverage NCD

Comment: One commenter noted that they thought research studies for gender reassignment surgery could not take place when the old NCD that prohibited coverage for gender reassignment surgery was in effect.

Response: CMS does not directly conduct clinical studies or pay for research grants. Some medical services are non-covered by Medicare; however, national non-coverage does not preclude research via a number of avenues and other funding entities such as the National Institutes of Health. In this instance, the previous NCD did not preclude interested parties from funding research for gender reassignment surgery that could have been generalizable to the Medicare population.

11. How the Medicare Population Differs from the General Population

Comment: One commenter questioned how the Medicare population differed from the general population, and why any differences would be important in our decision-making.

Response: The Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues.

12. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Comment: One commenter suggested CMS should have convened a MEDCAC for this topic.

Response: We appreciate the comment. Given the limited evidence, we did not believe a MEDCAC was warranted according to our guidance document entitled "Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee" (<https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html>).

13. §1557 of the Affordable Care Act (ACA)

Comment: Some commenters asserted that by not explicitly covering gender reassignment surgery at the national level, CMS was discriminating against transgender beneficiaries in conflict with Section 1557 of the Affordable Care Act (ACA).

Response: This decision does not affect the independent obligation of covered entities, including the Medicare program and MACs, to comply with Section 1557 in making individual coverage decisions. In accordance with Section 1557, MACs will apply neutral nondiscriminatory criteria when making case-by-case coverage determinations related to gender reassignment surgery.

14. Medicaid

Comment: Some commenters observed that some states cover gender reassignment surgery through Medicaid or require commercial insurers operating in the state to cover the surgery.

Response: We appreciate the information about Medicaid and state requirements; however, State decisions are separate from Medicare coverage determinations. We make evidence-based determinations based on our statutory standards and processes.

15. Commercial Insurers

Comment: In several instances, commenters told us that the healthcare industry looks to CMS coverage determinations to guide commercial policy coverage.

Response: CMS makes evidence-based national coverage determinations based on our statutory standards and processes as defined in the Social Security Act, which may not be the same standards that are used in commercial insurance policies or by other health care programs. In addition as noted above, the Medicare population is different (e.g., Medicare covers 95% of adults 65 and older) than the typical population under

16. Healthcare for Transgender Individuals

Comment: Numerous professional associations wrote to CMS to explain their support for access to healthcare for transgender individuals.

Response: CMS recognizes that transgender beneficiaries have specific healthcare needs. Many health care treatments are available. We encourage all beneficiaries to utilize their Medicare benefits to help them achieve their best health.

17. Intended Use of the Decision Memorandum

Comment: Several commenters expressed concern that the analysis provided in the proposed and final decision memorandums may be used by individuals, entities, or payers for purposes unrelated to Medicare such as denial of coverage for transgender-related surgeries.

Response: The purpose of the decision memoranda is to memorialize CMS' analysis of the evidence, provide responses to the public comments received, and to make available the clinical evidence and other data used in making our decision consistent with our obligations under the § 1862 of the Act. The NCD process is open and transparent and our decisions are publicly available. Congress requires that we provide a clear statement of the basis for our determinations. The decision memoranda are an important part of the record of the NCD. Our focus is the Medicare population which, as noted above, is different than the general population in a number of ways. Other entities may conduct separate evidence reviews and analyses that are suited for their specific populations.

18. Cost Barriers to Care and Effects

Comment: A few commenters stated that without Medicare coverage, surgery is difficult to afford and there may be a risk of negative consequences for the individual. One commenter suggested that CMS should consider prior-authorization for these surgeries.

Response: CMS is aware that paying out-of-pocket for medical care is a strain on a beneficiary's finances. We are also aware of beneficiaries' hesitancy to undergo surgery prior to knowing whether or not Medicare will pay the claim. Gender reassignment surgeries are not the only procedures whereby payment is not determined until after the provider submits the claim to Medicare. Importantly, documentation for the claims need to be explicit about what procedures were performed and include the appropriate information in the documentation to justify using the code or codes for surgery. Of note, CMS has claims data that indicate Medicare has paid for gender reassignment surgeries in the recent past. Determining which services are designated for prior-authorization is outside of the scope of the NCA process.

19. Surgical Risks and Benefits

Comment: A number of commenters conveyed the benefits of gender reassignment surgery, while other commenters expressed concern that gender reassignment surgery was harmful.

Response: We appreciate these comments.

20. Expenditure of Federal Funds

Comment: Some commenters opposed spending Medicare program funds on gender reassignment surgery for a variety of reasons. For example, some commenters believe it is an "elective" procedure. Other commenters suggested that funds should first be spent on other priorities such as durable medical equipment (DME) or mobility items such as power chairs; increasing reimbursement to providers; or that spending should be limited to the proportion to the transgender adult population in the Medicare program.

Response: The purpose of this NCA is to determine whether or not CMS should issue a NCD to cover surgery for patients who have gender dysphoria. NCAs do not establish payment amounts or spending priorities and, therefore, these comments are outside the scope of this consideration.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage.

Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that “[t]he Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.” *Heckler v. Ringer*, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

CMS carefully considered all the studies listed in this decision memorandum to determine whether they answered the question posed in this NCA. While there appears to be many publications regarding gender reassignment surgery, it became clear that many of the publications did not meet our inclusion/exclusion criteria as explained earlier in the decision memorandum.

Thirty-three papers were eligible based on our inclusion/exclusion criteria for the subsequent review (Figure 1). All studies reviewed had potential methodological flaws which we describe below.

A. Quality of the Studies Reviewed

Overall, the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding (a situation where the association between the intervention and outcome is influenced by another factor such as a co-intervention), small sample sizes, lack of validated assessment tools, and considerable lost to follow-up (Appendices C and F). The impact of a specific therapeutic intervention can be difficult to determine when there are multiple serial treatments such as psychotherapy, hormone treatment and surgery. To reduce confounding, outcome assessment just prior to and after surgery such as in a longitudinal study would be helpful. The objective endpoints included psychiatric treatment, attempted suicide, requests for surgical reversal, morbidity (direct and indirect adverse events), and mortality (Appendix F). CMS agrees with the utility of these objective endpoints. Quality of life, while important, is more difficult to measure objectively (Appendix E).

Of the 33 studies reviewed, published results were conflicting – some were positive; others were negative. Collectively, the evidence is inconclusive for the Medicare population. The majority of studies were non-longitudinal, exploratory type studies (i.e., in a preliminary state of investigation or hypothesis generating), or did not include concurrent controls or testing prior to and after surgery. Several reported positive results but the potential issues noted above reduced strength and confidence. After careful assessment, we identified six studies that could provide useful information (Figure 1). Of these, the four best designed and conducted studies that assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies did not demonstrate clinically significant changes or differences in psychometric test results after GRS. (Heylens et al., 2014; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008) (Appendix C Panel A and Appendix G.)

Two studies (three articles) assessed functional endpoints (request for surgical reassignment reversal and morbidity/mortality) (Dhejne et al., 2011; Dhejne et al., 2014 along with Landén et al., 1998) (Figure 1 and Appendix C, Panel A and Appendix G). Although the data are observational, they are robust because the Swedish national database is comprehensive (including all patients for which the government had paid for surgical services) and is notable for uniform criteria to qualify for treatment and financial coverage by the government. Dhejne et al. (2014) and Landén et al. (1998) reported cumulative rates of requests for surgical reassignment reversal or change in legal status of 3.3% while Dhejne et al. (2014) reported 2.2%. The authors indicated that the later updated calculation had the potential to be an underestimate because the most recent surgical cohorts were larger in size and had shorter periods of follow-up.

Dhejne et al., (2011) tracked all patients who had undergone reassignment surgery (mean age 35.1 years) over a 30 year interval and compared them to 6,480 matched controls. The study identified increased mortality and psychiatric hospitalization compared to the matched controls. The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. We note, mortality from this patient population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Further, we cannot exclude therapeutic interventions as a cause of the observed excess morbidity and mortality. The study, however, was not constructed to assess the impact of gender reassignment surgery *per se*.

We believe at minimum study designs should have a pre-test/post-test longitudinal design accompanied by characterization of all patients lost to follow-up over the entire treatment series as well as those patients who did not complete questionnaires, and the use of psychometric quality-of-life tools which are well validated with linkage to “hard” (objective) patient outcomes in this particular patient population (Trentacosti 2007, PRO 2009) (Appendices C and D).

Patient Care

Clinical evidentiary questions regarding the care of patients with gender dysphoria remain. Many of the publications focused on aspects of surgical technique as opposed to long-term patient outcomes. The specific type(s) of gender/sex reassignment surgery (e.g., genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific types of surgical procedures under study. Furthermore, surgical techniques have changed significantly over the last 60 years and may not reflect current practice (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations present a general framework and guidance on the care of the transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH notes, “More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.” Appendix D in the WPATH Standards of Care briefly describes their evidence base and acknowledges the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care rather than gender reassignment surgery was often the main focus. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

Psychometric Tools

CMS reviewed psychometric endpoints because gender dysphoria (inclusive of prior nomenclature) describes an incongruence between the gender assigned at birth and the gender(s) with which the person identifies.

The psychometric tools used to assess outcomes have limitations. Most instruments that were specific for gender dysphoria were designed by the investigators themselves or by other investigators within the field using limited populations and lacked well documented test characterization. (Appendices E and F) By contrast, test instruments with validation in large populations were non-specific and lacked validation in the gender dysphoric patient populations. (Appendices E and F). In addition, the presentation of psychometric results must be accompanied by enough information about the test itself to permit adequate interpretation of test results. The relevant diagnostic cut-points for scores and changes in scores that are clinically significant should also be scientifically delineated for interpretation.

Generalizability

It is difficult to generalize these study results to the current Medicare population. Many of the studies are old given they were conducted more than 10 years ago. Most of these studies were conducted outside of the U.S. in very different medical systems for treatment and follow-up. Many of the programs were single-site centers without replication elsewhere. The study populations were young and without significant physical or psychiatric co-morbidity (Appendix D). As noted earlier, psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landén et al., 1998).

Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. This review has identified gaps in the evidentiary base as well as recommendations for good study designs. The Institute of Medicine, the National Institutes of Health, and others also identified many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps. These gaps have been delineated as they represent areas in which patient care can be optimized and are opportunities for much needed research.

B. Health Disparities

Four studies included information on racial or ethnic background. The participants in the three U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants

in the single Asian study were Chinese (Isoy, 1993). Additional research is needed in this area.

C. Summary

Based on an extensive assessment of the clinical evidence as described above, there is not enough high quality evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively.

The knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines. Additional research of contemporary practice is needed. To assess long-term quality of life and other psychometric outcomes, it will be necessary to develop and validate standardized psychometric tools in patients with gender dysphoria. Further, patient preference is an important aspect of any treatment. As study designs are completed, it is important to include patient-centered outcomes.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We have received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination on whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery would be reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination relating to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 <i>Chapter: Psychosexual Disorders</i>	<i>Trans-sexualism</i> <i>302.5x [Gender Identity Disorder of Child-hood (302.6)]</i>	Required A (cross- gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III-Revised 1987 <i>TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence</i>	Trans-sexualism (TS) (302.50) <i>[GID of C]</i>	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1° and 2° sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-transsexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood , non-trans-sexual type, added			
DSM IV 1994 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex •Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM IV-Revised 2000 <i>Chapter: Sexual & Gender Identity Disorders</i>	Gender Identity Disorder (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6

DSM Version	Condition Name	Criteria	Criteria	Comments
			•e.g., frequent passing as the other sex - Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1^o and 2^o sex characteristics &/or acquiring sexual traits of the other sex - Clinically significant distress or impairment in social, occupational, or other important areas of functioning	•e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 <i>Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders</i>	Gender Dysphoria (302.85)	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	•Marked discordance between natal 1^o and 2^o sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1^o and 2^o sex characteristics** •Marked desire to acquire 1^o and 2^o sex characteristics of the other sex (or some alternative gender) - Clinically significant distress or impairment in social, occupational, or other important areas of functioning * or in young adolescents, the anticipated 2^o sex characteristics ** or in young adolescents, prevent the development of the anticipated 2^o sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: •Strong desire to be of the other gender or an insistence that one is of another gender.	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

DSM Version	Condition Name	Criteria	Criteria	Comments
			•Strong preference for cross-gender roles in make-believe play. •Strong preference for the toys, games, or activities of the other gender. •Strong preference for playmates of the other gender. •In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing •In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1^o=primary 2^o=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	804 w GD	324	324 (100%)	-
Dhejne 2014 Landén	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 50 were excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, & 16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1 & 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional		40	10 (25%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	Controlled	14 excluded for demographic matching reasons			The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual relationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender identity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional		119	119 (100%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.			Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results ¹⁰³ .
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal		1331	1177 (88.4%)	-

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No analysis by tx status	The number in the available patient pool was not specified.			
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference

B/C=because

BSRI=Bem Sex Role Inventory

F=Female

FP-R=Freiberg Personality Inventory

GD=Gender dysphoria

GID=Gender identity disorder

HADS=Hospital Anxiety & Depression Scale

IPP=Inventory of Interpersonal Problems

M=Male

NA=Not applicable

SCL-90=Symptom Checklist-90

SF-36=Short Form 36

GRS=Sex reassignment surgery

Tx=Treatment

W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery: 50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian

Author	Age (years, mean, S.D., range)	Gender	Race
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3±8.7 (20-62), M to F 36.3±10.1(21-69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landén	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7±4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M to F; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).		-

Author	Age (years, mean, S.D., range)	Gender	Caucasian
		W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio 1:1.6.	
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16-56), M to F: 31.4±11.4 (16-76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F to M: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve <i>Smilkstein</i>	Published in 1978 Initial data: 152 families in the U.S. A "friends" component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory <i>Beck, Ward, Mendelson, Mock, & Erbaugh</i>	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. It is copyrighted and requires a fee for use
Bem Sex Role Inventory <i>Bem</i>	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire <i>Clement & Lowe</i>	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale <i>Lindgren & Pauly</i> <i>(Kuiper, Dutch adaptation 1991)</i>	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire)	Developed circa 1966 Manual published 1970

Instrument Name and Developer	Development and Validation Information
<i>Crown & Crisp</i>	Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey <i>Anderson, Mikulić, Vermeylen, Lyly-Yrjanainen, & Zigante,</i>	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index <i>Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen</i>	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Körpers <i>Strauss</i>	Published 1996 (German)
Freiberg Personality Inventory <i>Fahrenberg, Hampel, & Selg</i>	7 th edition published 2001, 8 th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" <i>Smith, van Goozen, Kuiper, & Cohen-Kettenis</i>	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale <i>Altstotter-Gleich</i>	Published 1989 (German)
General Health Questionnaire <i>Goldberg & Blackwell (initial study)</i> <i>Goldberg & Williams (manual)</i>	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale <i>Zigmond & Snaith</i>	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1 st 50 compared to 2 nd 50.
Inventory of Interpersonal Problems <i>Horowitz</i>	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psychotherapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire <i>Kelleher, Cardozo, Khullar, & Salvatore</i>	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory <i>Hathaway & McKinley</i>	Published in 1941 Updated in 1989 with new, larger, more diverse sample.

Instrument Name and Developer	Development and Validation Information
<i>Butcher, Dahlstrom, Graham, & Tellegen</i>	MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphilia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" <i>Doorn, Kuiper, Verschoor, Cohen-Kettenis</i>	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences <i>Wolfradt</i>	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" <i>Cohen-Kettenis & van Goozen</i>	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale <i>Rosenberg</i>	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 <i>RAND</i> <i>Ware & Sherbourne 1992</i> <i>McHorney, Ware, & Raczek 1993</i>	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale <i>Watson & Friend</i>	Initial publication in 1969 Requires permission for use
Social Support Scale <i>Van Tilburg 1988</i>	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire <i>Spielberger, Gorsuch, Lushene, Vagg, & Jacobs</i>	Current format published in 1983 Proprietary test
Symptom Checklist-90 <i>Derogatis, Lipman, Covi</i> <i>Derogatis & Cleary</i>	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale <i>Fitts & Warren</i>	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other information available. Requires qualification for use
Utrecht Gender Dysphoria Scale <i>Cohen-Kettenis & van Goozen</i>	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)

Instrument Name and Developer	Development and Validation Information
WHO-Quality of Life (abbreviated version) <i>Harper for WHO group</i>	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landén	Yes	-	-	-	Includes demographics*	Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS, STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscherman et al.	Yes	-	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2 nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Körpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 ($\pm$ R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.**Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets**

Author	Test	Patient and Data Loss	Results
Psychometric Test			
Heylens et al. Belgium 2014	SCL-90R	90 applicants for SRS were recruited. •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx. •12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical comorbidity, personal decision for no tx, or personal decision for only hormone tx. •1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. •1 (12.2% of initial recruits) had not yet received SRS by study close. 46 (51.1% of recruited) underwent serial evaluation •The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) missing data for another 1.1% to 11.1%.	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.
Ruppin,Pfafflin, Germany 2015	SCL-90R	The number in the available patient pool was not specified.	

Author	Test	Patient and Data Loss	Results
		140 received recruitment letters. •2 (1.4% of those with recruitment letters) had died. •1 (0.7%) was institutionalized. •5 (3.6%) were ill. •8 (5.7%) did not have time. •8 (5.7%) stated that GD was no longer an issue. •8 (5.7%) provided no reason. •28 (20.0%) declined further contact. •9 (6.4%) were lost to follow-up. 71 (50.7%) agreed to participate. •2 (1.4%) had not undergone SRS •The test was not completed by 9. missing data for another 6.4%.	At t=0, the "global severity index "SCL-90R score was 0.53 ± 0.49. At post-SRS follow-up the score had decreased to 0.28 ± 0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70 ± 0.67 at t=0 and 0.26 ± 0.34 post-SRS.
Smith et al. Holland 2005	MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. •103 (31.7%) were not eligible to start hormone tx & real-life experience. •34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. •36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0 ± 40.7. At post SRS-follow-up, the score had decreased to 120.3 ± 31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. •Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.

Author	Test	Patient and Data Loss	Results
			There were no statistically significant changes in the global score or for any of the subscales.
National Databases			
Dehjne Sweden 2011	Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. •480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. •All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9-8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0-3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landén et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. •All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID=NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery
Tx=Treatment [Back to Top](#)

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID:> 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstötter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentität* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid- Technique as shown at the example of the assessment of gender identity], Verlag für empirische Pädagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients.* 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5& 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to- male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry.* 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Gooren LJ, Eklund PC. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism*. 1989 Sep;38(9):869-73. PMID: 2528051.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel- Journeel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia*. 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004 June;328(19):1490-4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA*. 2010 Summer-Fall;22 (4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med*. 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristoni J, Menggola MC, Jannini EA, Mannelli C, Corona G, Mercurio M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res*. 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013 Mar;13(3):214- 22. Epub 2012 Dec 21. PMID: 23260128.

Barlow DH, Abel GG, Blanchard EB. Gender identity change in transsexuals. Follow-up and replications. *Arch Gen Psychiatry*. 1979 Aug;36(9):1001-7. PMID: 464738.

Barrett J. (1998) *Psychological and social function before and after phalloplasty*. University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or *IJT*. 1998; 2:1 or <http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal..pdf>.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav*. 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav*. 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med* .2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

Baumeister S, Sohn M, Donike C, Exner K. [Phalloplasty in female-to-male transsexuals: experience from 259 cases]. *Handchir Mikrochir Plast Chir.* 2011 Aug;43(4):215-21. Epub 2011 Aug 11. PMID: 21837614.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis.* 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to- female transsexualism. *Fertil Steril.* 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril.* 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology.* 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg.* 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third> sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol.* 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheoran B, Sheth L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav*. 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes*. 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), *Gender dysphoria: Development, research, management* (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav*. 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry*. 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med*. 2011 Jun 30;364 (26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow- up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25 (3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health.* 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am.* 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med.* 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev*. 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics*. 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav*. 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)*. 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav*. 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth*. 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self- injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med*. 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol*. 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex*. 2006;51(3):53-69. PMID: 17135115.

CMS Office of Minority Health. New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. 2015. Academy Health Annual Research Meeting, Minneapolis, Minnesota.

CMS Office of Minority Health. If You Build It, They Will Come: Accessing and Utilizing HHS LGBTI Data and Information Products. 2015. Gay and Lesbian Medical Association Meeting, Portland, Oregon.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry*. 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res*. 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT. Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress

in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10. PMID: 25691225.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R, Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend*. 2011;13:165-232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from

a household probability sample of adults. *Am J Public Health*. 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol*. 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women's souls: Personal narrative of Thailand's transgendered youth*. Routledge.

Costantino A, Cerpomini S, Alvisi S, Morselli P, Venturini S, Meriggiani M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther.* 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148- 53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry.* 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril.* 2010 Dec;94 (7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. [February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf](http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf).

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav.* 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry.* 2007 Apr;22(3):137- 41. Epub 2006 Dec 26. PMID: 17188846.

Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male- to-female transsexual after initiation of hormone therapy. *J Clin Neurosci.* 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull.* 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci.* 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry.* 1974;7(0):79- 110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol.* 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis.* 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gynecol*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186 (2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6 (2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav*. 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol*. 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male- to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes*. 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduyn T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*. 2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav*. 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol*. 2011 Jun;51 (2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis*. 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan- Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub*. 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinic D, Barisic V, Djordjevic ML, Vujovic S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal*. 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72 (1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg*. 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20 (6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikulić B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview*. EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrac M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work*. EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Ferring D, Filipp SH. Messung des Selbstwertgefühls: Befunde zu Reliabilität, Validität und Stabilität der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica*. 1996; 42: 284–292. German. (Not in PubMed)

Ferron P, Young S, Boulanger C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med*. 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Flores A, Herman J, Gates G, Brown T. (2016) *How many adults identify as transgender in the United States?* Los Angeles, CA: The Williams Institute.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry*. 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab.* 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexualsurgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir.* 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res.* 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav.* 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl.* 2011 May;13 (3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol.* 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev.* 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol.* 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril.* 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand*. 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165 (4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Gates GJ. How many people are lesbian, gay, bisexual, and transgender? 2011. (Not in PubMed) williamsinstitute@law.ucla.edu.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNeil D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law*. 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med*. 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int*. 2007 Sep;100(3):607-13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website: <http://www.stat.berkeley.edu/users/hhuang/141C-2008.html>. Section Website: <http://www.stat.berkeley.edu/users/mgoldman>.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess*. 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav*. 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav*. 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav*. 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero- Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res.* 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res.* 2005;64 Suppl 2:31-6. PMID: 16286768.

Gooren L. Clinical practice. Care of transsexual persons. *N Engl J Med.* 2011 Mar 31;364(13):1251-7. PMID: 21449788.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia.* 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes.* 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross- sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol.* 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med.* 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia.* 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebieux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med.* 2012 Feb;9 (2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self- esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis.* 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict.* 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res.* 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol.* 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis.* 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment.* 1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonasate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav.* 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and> strength of recommendations. *BMJ.* 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ*. 2008 May 3;336(7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652):1049-51. Erratum in: *BMJ*. 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011 Apr;64(4):395-400. Epub 2010 Dec 30. PMID: 21194891.

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol*. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol*. 2011 Dec;64(12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian,

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery*. 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand*. 2000 Oct;102(4):276- 81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry*. 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13 (4):364-8. PMID: 13463138.

Hathaway SR, Reynolds PC, Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hebbar S, Pandey H, Chawla A. Understanding King's Health Questionnaire (KHQ) in assessment of female urinary incontinence. *Int J Res Med Sci* 2015;3:531-8.

Hembree WC, Cohen-Kettenis P, Delamaré-Van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt*. 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res*. 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry*. 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics/objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services. Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology*. 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel)*. 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand*. 1971;47 (1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel)*. 1973;6(2):65- 80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat*. 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21; (1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med*. 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol*. 1988 Dec;56 (6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci*. 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav*. 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav*. 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile intranssexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B- Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha- reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013.
<http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml>.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry*. 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. <http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf>.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex*. 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol*. 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS*. 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltán R, Kawaciuk I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med*. 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav*. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal*. 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab*. 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co- morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hoer C, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav.* 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci.* 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics.* 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav.* 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child.* 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav.* 1987 Dec;16(6):511-22. PMID: 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav.* 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences.* Stanford, Calif.: Stanford University Press, 1966.

Krege S, Bex A, Lümnen G, Rübber H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollner H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol*. 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hildebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol*. 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril*. 2009 Nov;92(5):1685-1689.e3. Epub

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ*. 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5: DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician*. 2013 Oct 15;88(8):Online. PMID: 24364581.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res*. 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation*. 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet*. 2011 April 9;377: 1211. PMID:2 1481690.

A - Landén M, Wålinder J, Lambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand*. 1998 Apr;97(4):284-9. PMID: 9570489.

B - Landén M, Walinder J, Lundstrom B. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. *Acta Psychiatr Scand* 1998; 97: 189-194.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol*. 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav*. 1999 Dec;28(6):581-3. PMID: 10650442.

Lawrence A. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav*. 2003 Aug;32(4):299-315. PMID: 12856892.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav*. 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav*. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Arch Sex Behav.* 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoepfner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract.* 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lief HI, Hubschman L. Orgasm in the postoperative transsexual. *Arch Sex Behav.* 1993 Apr;22 (2):145-55. PMID: 8476334.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav.* 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand.* 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav.* 1975 Nov;4(6):639-56. PMID: 1212093.

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav.* 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav.* 1979 Sep;8 (5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav.* 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess.* 1984 Oct;48 (5):500-7. PMID: 6389823.

Lundström B, Pauly I, Wålinder J. Outcome of sex reassignment surgery. *Acta Psychiatr Scand.* 1984 Oct;70(4):289-94. PMID: 6388248.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev.* 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D,

Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grütters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5 α -reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab.* 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Matarix-Cole D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav*. 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry*. 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry*. 1990 Aug;157:261-4. PMID: 2224377.

Maycock L, Kennedy H. Breast care in the transgender individual. *J Midwifery Womens Health*. 2014 Jan-Feb;59(1):74-81. Epub 2013 Nov 13. PMID: 24224502.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med*. 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database*. 2009. No.3. www.birmingham.ac.uk/Documents/college-

Medraś M, Józków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol.* 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy.* 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health.* 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self- prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med.* 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Jannini E, Lenzi A, Maggi M, Manieri C. Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. *Eur J Endocrinol.* 2010 May;162(5):831-3. Epub 2010 Feb 11. PMID: 20150325.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl.* 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf).* 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):607- 15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

D- Meyer JK. Clinical variants among applicants for sex reassignment. *Arch Sex Behav*. 1974 Nov;3 (6):527-58. PMID: 4429437.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10 (4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav*. 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am*. 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Anseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miles C, Green R, Hines M. Estrogen treatment effects on cognition, memory and mood in male-to- female transsexuals. *Horm Behav*. 2006 Dec;50(5):708-17. Epub 2006 Aug 1. PMID: 16884726.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics*. 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient- subjects. *J Med Ethics*. 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol*. 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg*. 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr*. 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. Spanish. PMID: 22542505.

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med*. 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav*. 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollner H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med*. 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Muller RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

NIH FY 2016-2020 Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities. 2015 http://edi.nih.gov/sites/default/files/EDI_Public_files/sgm-strategic-plan.pdf

NIH-LGBT 2013: National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care*. 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015*. (Portland State quantitative methods)www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter-Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med.* 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. *J Acquir Immune Defic Syndr.* 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health* 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health.* 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery*. New Zealand Health technology Assessment. (NZHTA). The clearinghouse for health outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

Odgaard-Jensen J, Vist GE, Timmer A, Kunz R, Akl EA, Schünemann H, Briel M, Nordmann AJ, Pregno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev.* 2011 Apr 13;(4):MR000012. PMID: 21491415.

O'Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J.* 1981;50 (1):46-9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res.* 2008 Jan 15;157 (1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med.* 2011 Feb;165(2):171-6. PMID: 21300658.

surgical treatment. *World J Psychiatry*. 1996;56(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav*. 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long- term follow-up. *Arch Sex Behav*. 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr*. 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav*. 2011 Apr;15(3):674-82. PMID: 21604064.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex*. 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögenderfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to- male transsexuals. *J Sex Med*. 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res*. 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to- female transsexual persons. *J Voice*. 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology*. 2005 Jul;16 (4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis*. 1968 Nov;147(5):460- 71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15 (1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril*. 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med*. 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work*. 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 May 23;7:9. PMID: 22621419.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims. December 2009.* <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf>.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To- Male Genital Reconstructive Surgery. *IJT*. 1999 Jul-Sept;3(3). (Not in PubMed) <http://www.symposion.com/ijt/ijt990302.htm>

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res*. 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarrre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res*. 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J*. 1959 Dec 26; 2 (5164): 1448-52. PMID: 14436154.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):Trans-sexualism and Sex reassignment. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res*. 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav*. 1999 Feb;28(1):71-89. PMID: 10097806.

Reisner S, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, Holland C, Max R, Baral S. Global health burden and needs of transgender populations: a review. *Lancet*. Epub 16 June 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)00684-X](http://dx.doi.org/10.1016/S0140-6736(16)00684-X)

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand*. 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav*. 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl*. 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav*. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health*. 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract*. 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18 (88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci*. 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193-236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carter RA. New Women: Sexological outcomes of male-to-female gender reassignment surgery. *JSET*. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclair C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg*. 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol*. 2011 May;8 (5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol*. 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer*. 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law*. 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology*. 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT*. 2001 Jul-Sept; 5(3):20 pages.http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev*. 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract*. 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract*. 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2001 Apr;40(4):472-81. PMID: 11314574.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med*. 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res*. 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand*. 1981 May;63 (5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand*. 1981 Jul;64 (1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav* 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):192-206Epub 2010 Mar 29. PMID: 20347346.

Steinle K. Hormonal management of the female-to-male transgender patient. *J Midwifery Womens Health*. 2011 May-Jun;56(3):293-302. PMID: 21535376.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav*. 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J*. 1972 Mar;68 (3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat*. 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBek), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev*. 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills*. 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol*. 2004 Dec;19(6):301-12. PMID: 15724806.

Swaab DF, Garcia-Falgueras A. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Funct Neurol*. 2009 Jan-Mar;24(1):17-28. PMID: 19403051.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res*. 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res*. 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female- to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand*. 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman J. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom*. 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav*. 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry*. 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand*. 1988 Oct;78 (4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J*. 1992 Apr;33(2):162-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J*. 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore*. 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess*. 1979. Aug;43(4):385-7. PMID: 383946.

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007 Oct;83(984):638-42. PMID: 17916872.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol*. 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol*. 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedeker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab*. 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsson T, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierzak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med*. 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity in Flanders, Belgium. *Arch Sex Behav*. 2015 Jul;44 (5):1281-7. Epub 2015 Jan 15. PMID: 25588709.

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav*. 2013; 42:361-70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav*. 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med*. 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med*. 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mrvošević Marojević L, Ivović M, Tančić-Gajić M, Stojanović M, Marina LV, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal*. 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow-up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry*. 1978;132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. *Lancet*. Epub 16 June 2016 [http://dx.doi.org/10.1016/S0140-6736\(16\)00683-8](http://dx.doi.org/10.1016/S0140-6736(16)00683-8)

Weigert R, Frison E, Sessieq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med*. 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology*. 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quality of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people. Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV*. World Health Organization. July 2015. <http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/>.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther*. 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van de Peer F, Dedeker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedeker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

Wylie K, Knudson G, Khan S, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet*. Epub 16 June 2016. [http://dx.doi.org/10.1016/S0140-6736\(16\)00682-6](http://dx.doi.org/10.1016/S0140-6736(16)00682-6)

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedeker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod*. 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med*. 2012 Oct;9(10):2641- 51. Epub 2012 Aug 20. PMID: 22906135.

C-Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav*. 2012 Oct;41(5):1069-71. PMID: 22968492.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med*. 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction.* 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health.* 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex.* 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S. The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract.* 1999; 49 (449): 991-2. PMID: 10824346.

Wilson RC, Nimkarn S, Domic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic- specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21- hydroxylase deficiency. *Mol Genet Metab.* 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab.* 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect.* 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol.* 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav*. 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol*. 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav*. 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders*. (6th version) February, 2001.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012.
http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr*. 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez- Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab*. 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals*. (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5 α -Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopoulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg*. 2006 May;77(5):432-8. German. Erratum in *Chirurg*. 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis*. 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry*. 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res*. 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901-14. PMID: 23868018.

EXHIBIT H



WPATH WORLD PROFESSIONAL
ASSOCIATION for
TRANSGENDER HEALTH

Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People

The World Professional Association for Transgender Health

Standards of Care

for the Health of Transsexual, Transgender, and Gender Nonconforming People

The World Professional Association for Transgender Health

7th Version¹ | www.wpath.org

¹ This is the seventh version of the Standards of Care. The original SOC were published in 1979. Previous revisions were in 1980, 1981, 1990, 1998, and 2001.

Table of Contents

I. Purpose and Use of the Standards of Care	1
II. Global Applicability of the Standards of Care	3
III. The Difference between Gender Nonconformity and Gender Dysphoria	4
IV. Epidemiologic Considerations	6
V. Overview of Therapeutic Approaches for Gender Dysphoria	8
VI. Assessment and Treatment of Children and Adolescents with Gender Dysphoria	10
VII. Mental Health	21
VIII. Hormone Therapy	33
IX. Reproductive Health	50
X. Voice and Communication Therapy	52
XI. Surgery	54
XII. Postoperative Care and Follow-Up	64
XIII. Lifelong Preventive and Primary Care	65
XIV. Applicability of the <i>Standards of Care</i> to People Living in Institutional Environments . . .	67
XV. Applicability of the <i>Standards of Care</i> to People With Disorders of Sex Development . .	69

References	72

Appendices:

A. Glossary	95
B. Overview of Medical Risks of Hormone Therapy	97
C. Summary of Criteria for Hormone Therapy and Surgeries	104
D. Evidence for Clinical Outcomes of Therapeutic Approaches	107
E. Development Process for the <i>Standards of Care, Version 7</i>	109

Purpose and Use of the Standards of Care

The World Professional Association for Transgender Health (WPATH)¹ is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect for transgender health. The vision of WPATH is to bring together diverse professionals dedicated to developing best practices and supportive policies worldwide that promote health, research, education, respect, dignity, and equality for transsexual, transgender, and gender nonconforming people in all cultural settings.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the articulation of *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*. The SOC are based on the best available science and expert professional consensus.² Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC to other parts of the world are necessary. Suggestions for ways of thinking about cultural relativity and cultural competence are included in this version of the SOC.

The overall goal of the SOC is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. This assistance may include primary care, gynecologic and urologic care, reproductive options, voice and communication therapy, mental health services (e.g., assessment, counseling, psychotherapy), and hormonal and surgical treatments. While this is primarily a document for health professionals, the SOC may also be used by individuals, their families, and social institutions to understand how they can assist with promoting optimal health for members of this diverse population.

WPATH recognizes that health is dependent upon not only good clinical care but also social and political climates that provide and ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that promote tolerance and equity

1 Formerly the Harry Benjamin International Gender Dysphoria Association

2 *Standards of Care (SOC), Version 7* represents a significant departure from previous versions. Changes in this version are based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender nonconforming people beyond hormone therapy and surgery (Coleman, 2009a, b, c, d).

for gender and sexual diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these changes in public policies and legal reforms.

The Standards of Care Are Flexible Clinical Guidelines

The SOC are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria – broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

As for all previous versions of the SOC, the criteria put forth in this document for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care – and the SOC – to evolve.

The SOC articulate standards of care but also acknowledge the role of making informed choices and the value of harm reduction approaches. In addition, this version of the SOC recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Some patients who present for care will have made significant self-directed progress towards gender role changes, transition, or other resolutions regarding their gender identity or gender dysphoria. Other patients will require more intensive services. Health professionals can use the SOC to help patients consider the full range of health services open to them, in accordance with their clinical needs and goals for gender expression.



Global Applicability of the Standards of Care

While the SOC are intended for worldwide use, WPATH acknowledges that much of the recorded clinical experience and knowledge in this area of health care is derived from North American and Western European sources. From place to place, both across and within nations, there are differences in all of the following: social attitudes towards transsexual, transgender, and gender nonconforming people; constructions of gender roles and identities; language used to describe different gender identities; epidemiology of gender dysphoria; access to and cost of treatment; therapies offered; number and type of professionals who provide care; and legal and policy issues related to this area of health care (Winter, 2009).

It is impossible for the SOC to reflect all of these differences. In applying these standards to other cultural contexts, health professionals must be sensitive to these differences and adapt the SOC according to local realities. For example, in a number of cultures, gender nonconforming people are found in such numbers and living in such ways as to make them highly socially visible (Peletz, 2006). In settings such as these, it is common for people to initiate a change in their gender expression and physical characteristics while in their teens, or even earlier. Many grow up and live in a social, cultural, and even linguistic context quite unlike that of Western cultures. Yet almost all experience prejudice (Peletz, 2006; Winter, 2009). In many cultures, social stigma towards gender nonconformity is widespread and gender roles are highly prescriptive (Winter et al., 2009). Gender nonconforming people in these settings are forced to be hidden, and therefore may lack opportunities for adequate health care (Winter, 2009).

The SOC are not intended to limit efforts to provide the best available care to all individuals. Health professionals throughout the world – even in areas with limited resources and training opportunities – can apply the many core principles that undergird the SOC. These principles include the following: Exhibit respect for patients with nonconforming gender identities (do not pathologize differences in gender identity or expression); provide care (or refer to knowledgeable colleagues) that affirms patients' gender identities and reduces the distress of gender dysphoria, when present; become knowledgeable about the health care needs of transsexual, transgender, and gender nonconforming people, including the benefits and risks of treatment options for gender dysphoria; match the treatment approach to the specific needs of patients, particularly their goals for gender expression and need for relief from gender dysphoria; facilitate access to appropriate care; seek patients' informed consent before providing treatment; offer continuity of care; and be prepared to support and advocate for patients within their families and communities (schools, workplaces, and other settings).

Terminology is culturally and time-dependent and is rapidly evolving. It is important to use respectful language in different places and times, and among different people. As the SOC are translated into other languages, great care must be taken to ensure that the meanings of terms are accurately translated. Terminology in English may not be easily translated into other languages, and vice versa. Some languages do not have equivalent words to describe the various terms within this document; hence, translators should be cognizant of the underlying goals of treatment and articulate culturally applicable guidance for reaching those goals.



The Difference Between Gender Nonconformity and Gender Dysphoria

Being Transsexual, Transgender, or Gender Nonconforming Is a Matter of Diversity, Not Pathology

WPATH released a statement in May 2010 urging the de-psychopathologization of gender nonconformity worldwide (WPATH Board of Directors, 2010). This statement noted that “the expression of gender characteristics, including identities, that are not stereotypically associated with one’s assigned sex at birth is a common and culturally-diverse human phenomenon [that] should not be judged as inherently pathological or negative.”

Unfortunately, there is stigma attached to gender nonconformity in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in “minority stress” (I. H. Meyer, 2003). Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make transsexual, transgender, and gender nonconforming individuals more vulnerable to developing mental health concerns such as anxiety and depression (Institute of Medicine, 2011). In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and neglect in one’s relationships with peers and family members, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being transsexual, transgender, or gender nonconforming.

Gender Nonconformity Is Not the Same as Gender Dysphoria

Gender nonconformity refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex (Institute of Medicine, 2011). *Gender dysphoria* refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b). Only *some* gender nonconforming people experience gender dysphoria at *some* point in their lives.

Treatment is available to assist people with such distress to explore their gender identity and find a gender role that is comfortable for them (Bockting & Goldberg, 2006). Treatment is individualized: What helps one person alleviate gender dysphoria might be very different from what helps another person. This process may or may not involve a change in gender expression or body modifications. Medical treatment options include, for example, feminization or masculinization of the body through hormone therapy and/or surgery, which are effective in alleviating gender dysphoria and are medically necessary for many people. Gender identities and expressions are diverse, and hormones and surgery are just two of many options available to assist people with achieving comfort with self and identity.

Gender dysphoria can in large part be alleviated through treatment (Murad et al., 2010). Hence, while transsexual, transgender, and gender nonconforming people may experience gender dysphoria at some point in their lives, many individuals who receive treatment will find a gender role and expression that is comfortable for them, even if these differ from those associated with their sex assigned at birth, or from prevailing gender norms and expectations.

Diagnoses Related to Gender Dysphoria

Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder. Such a diagnosis is not a license for stigmatization or for the deprivation of civil and human rights. Existing classification systems such as the *Diagnostic Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2000) and the *International Classification of Diseases (ICD)* (World Health Organization, 2007) define hundreds of mental disorders that vary in onset, duration, pathogenesis, functional disability, and treatability. All of these systems attempt to classify clusters of symptoms and conditions, not the individuals themselves. A disorder is a description of something with which a person might struggle, not a description of the person or the person's identity.

Thus, transsexual, transgender, and gender nonconforming individuals are not inherently disordered. Rather, the distress of gender dysphoria, when present, is the concern that might be diagnosable and for which various treatment options are available. The existence of a diagnosis for such dysphoria often facilitates access to health care and can guide further research into effective treatments.

Research is leading to new diagnostic nomenclatures, and terms are changing in both the *DSM* (Cohen-Kettenis & Pfäfflin, 2010; Knudson, De Cuypere, & Bockting, 2010b; Meyer-Bahlburg, 2010; Zucker, 2010) and the *ICD*. For this reason, familiar terms are employed in the *SOC* and definitions are provided for terms that may be emerging. Health professionals should refer to the most current diagnostic criteria and appropriate codes to apply in their practice areas.

IV Epidemiologic Considerations

Formal epidemiologic studies on the incidence³ and prevalence⁴ of transsexualism specifically or transgender and gender nonconforming identities in general have not been conducted, and efforts to achieve realistic estimates are fraught with enormous difficulties (Institute of Medicine, 2011; Zucker & Lawrence, 2009). Even if epidemiologic studies established that a similar proportion of transsexual, transgender, or gender nonconforming people existed all over the world, it is likely that cultural differences from one country to another would alter both the behavioral expressions of different gender identities and the extent to which gender dysphoria – distinct from one's gender identity – is actually occurring in a population. While in most countries, crossing normative gender boundaries generates moral censure rather than compassion, there are examples in certain cultures of gender nonconforming behaviors (e.g., in spiritual leaders) that are less stigmatized and even revered (Besnier, 1994; Bolin, 1988; Chiñas, 1995; Coleman, Colgan, & Gooren, 1992; Costa & Matzner, 2007; Jackson & Sullivan, 1999; Nanda, 1998; Taywaditep, Coleman, & Dumronggittigule, 1997).

For various reasons, researchers who have studied incidence and prevalence have tended to focus on the most easily counted subgroup of gender nonconforming individuals: transsexual individuals who experience gender dysphoria and who present for gender-transition-related care at specialist gender clinics (Zucker & Lawrence, 2009). Most studies have been conducted in European

3 **incidence**—the number of new cases arising in a given period (e.g., a year)

4 **prevalence**—the number of individuals having a condition, divided by the number of people in the general population

countries such as Sweden (Wålinder, 1968, 1971), the United Kingdom (Hoenig & Kenna, 1974), the Netherlands (Bakker, Van Kesteren, Gooren, & Bezemer, 1993; Eklund, Gooren, & Bezemer, 1988; van Kesteren, Gooren, & Megens, 1996), Germany (Weitze & Osburg, 1996), and Belgium (De Cuypere et al., 2007). One was conducted in Singapore (Tsoi, 1988).

De Cuypere and colleagues (2007) reviewed such studies, as well as conducted their own. Together, those studies span 39 years. Leaving aside two outlier findings from Pauly in 1968 and Tsoi in 1988, ten studies involving eight countries remain. The prevalence figures reported in these ten studies range from 1:11,900 to 1:45,000 for male-to-female individuals (MtF) and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals. Some scholars have suggested that the prevalence is much higher, depending on the methodology used in the research (for example, Olyslager & Conway, 2007).

Direct comparisons across studies are impossible, as each differed in their data collection methods and in their criteria for documenting a person as transsexual (e.g., whether or not a person had undergone genital reconstruction, versus had initiated hormone therapy, versus had come to the clinic seeking medically-supervised transition services). The trend appears to be towards higher prevalence rates in the more recent studies, possibly indicating increasing numbers of people seeking clinical care. Support for this interpretation comes from research by Reed and colleagues (2009), who reported a doubling of the numbers of people accessing care at gender clinics in the United Kingdom every five or six years. Similarly, Zucker and colleagues (2008) reported a four- to five-fold increase in child and adolescent referrals to their Toronto, Canada clinic over a 30-year period.

The numbers yielded by studies such as these can be considered minimum estimates at best. The published figures are mostly derived from clinics where patients met criteria for severe gender dysphoria and had access to health care at those clinics. These estimates do not take into account that treatments offered in a particular clinic setting might not be perceived as affordable, useful, or acceptable by all self-identified gender dysphoric individuals in a given area. By counting only those people who present at clinics for a specific type of treatment, an unspecified number of gender dysphoric individuals are overlooked.

Other clinical observations (not yet firmly supported by systematic study) support the likelihood of a higher prevalence of gender dysphoria: (i) Previously unrecognized gender dysphoria is occasionally diagnosed when patients are seen with anxiety, depression, conduct disorder, substance abuse, dissociative identity disorders, borderline personality disorder, sexual disorders, and disorders of sex development (Cole, O'Boyle, Emory, & Meyer III, 1997). (ii) Some crossdressers, drag queens/kings or female/male impersonators, and gay and lesbian individuals may be experiencing gender dysphoria (Bullough & Bullough, 1993). (iii) The intensity of some people's gender dysphoria fluctuates below and above a clinical threshold (Docter, 1988). (iv) Gender nonconformity among FtM individuals tends to be relatively invisible in many cultures, particularly to Western health

professionals and researchers who have conducted most of the studies on which the current estimates of prevalence and incidence are based (Winter, 2009).

Overall, the existing data should be considered a starting point, and health care would benefit from more rigorous epidemiologic study in different locations worldwide.



Overview of Therapeutic Approaches for Gender Dysphoria

Advancements in the Knowledge and Treatment of Gender Dysphoria

In the second half of the 20th century, awareness of the phenomenon of gender dysphoria increased when health professionals began to provide assistance to alleviate gender dysphoria by supporting changes in primary and secondary sex characteristics through hormone therapy and surgery, along with a change in gender role. Although Harry Benjamin already acknowledged a spectrum of gender nonconformity (Benjamin, 1966), the initial clinical approach largely focused on identifying who was an appropriate candidate for sex reassignment to facilitate a physical change from male to female or female to male as completely as possible (e.g., Green & Fleming, 1990; Hastings, 1974). This approach was extensively evaluated and proved to be highly effective. Satisfaction rates across studies ranged from 87% of MtF patients to 97% of FtM patients (Green & Fleming, 1990), and regrets were extremely rare (1-1.5% of MtF patients and <1% of FtM patients; Pfäfflin, 1993). Indeed, hormone therapy and surgery have been found to be medically necessary to alleviate gender dysphoria in many people (American Medical Association, 2008; Anton, 2009; The World Professional Association for Transgender Health, 2008).

As the field matured, health professionals recognized that while many individuals need both hormone therapy and surgery to alleviate their gender dysphoria, others need only one of these treatment options and some need neither (Bockting & Goldberg, 2006; Bockting, 2008; Lev, 2004). Often with the help of psychotherapy, some individuals integrate their trans- or cross-gender feelings into the gender role they were assigned at birth and do not feel the need to feminize or masculinize their body. For others, changes in gender role and expression are sufficient to alleviate

gender dysphoria. Some patients may need hormones, a possible change in gender role, but not surgery; others may need a change in gender role along with surgery, but not hormones. In other words, treatment for gender dysphoria has become more individualized.

As a generation of transsexual, transgender, and gender nonconforming individuals has come of age – many of whom have benefitted from different therapeutic approaches – they have become more visible as a community and demonstrated considerable diversity in their gender identities, roles, and expressions. Some individuals describe themselves not as gender nonconforming but as unambiguously cross-sexed (i.e., as a member of the other sex; Bockting, 2008). Other individuals affirm their unique gender identity and no longer consider themselves either male or female (Bornstein, 1994; Kimberly, 1997; Stone, 1991; Warren, 1993). Instead, they may describe their gender identity in specific terms such as transgender, bigender, or genderqueer, affirming their unique experience that may transcend a male/female binary understanding of gender (Bockting, 2008; Ekins & King, 2006; Nestle, Wilchins, & Howell, 2002). They may not experience their process of identity affirmation as a “transition,” because they never fully embraced the gender role they were assigned at birth or because they actualize their gender identity, role, and expression in a way that does not involve a change from one gender role to another. For example, some youth identifying as genderqueer have always experienced their gender identity and role as such (genderqueer). Greater public visibility and awareness of gender diversity (Feinberg, 1996) has further expanded options for people with gender dysphoria to actualize an identity and find a gender role and expression that is comfortable for them.

Health professionals can assist gender dysphoric individuals with affirming their gender identity, exploring different options for expression of that identity, and making decisions about medical treatment options for alleviating gender dysphoria.

Options for Psychological and Medical Treatment of Gender Dysphoria

For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one’s gender identity);
- Hormone therapy to feminize or masculinize the body;

- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience.

Options for Social Support and Changes in Gender Expression

In addition (or as an alternative) to the psychological and medical treatment options described above, other options can be considered to help alleviate gender dysphoria, for example:

- Offline and online peer support resources, groups, or community organizations that provide avenues for social support and advocacy;
- Offline and online support resources for families and friends;
- Voice and communication therapy to help individuals develop verbal and non-verbal communication skills that facilitate comfort with their gender identity;
- Hair removal through electrolysis, laser treatment, or waxing;
- Breast binding or padding, genital tucking or penile prostheses, padding of hips or buttocks;
- Changes in name and gender marker on identity documents.

VI

Assessment and Treatment of Children and Adolescents with Gender Dysphoria

There are a number of differences in the phenomenology, developmental course, and treatment approaches for gender dysphoria in children, adolescents, and adults. In children and adolescents, a rapid and dramatic developmental process (physical, psychological, and sexual) is involved and

there is greater fluidity and variability in outcomes, particular in prepubertal children. Accordingly, this section of the SOC offers specific clinical guidelines for the assessment and treatment of gender dysphoric children and adolescents.

Differences between Children and Adolescents with Gender Dysphoria

An important difference between gender dysphoric children and adolescents is in the proportion for whom dysphoria persists into adulthood. Gender dysphoria during childhood does not inevitably continue into adulthood.⁵ Rather, in follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6-23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12-27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).

In contrast, the persistence of gender dysphoria into adulthood appears to be much higher for adolescents. No formal prospective studies exist. However, in a follow-up study of 70 adolescents who were diagnosed with gender dysphoria and given puberty suppressing hormones, all continued with the actual sex reassignment, beginning with feminizing/masculinizing hormone therapy (de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2010).

Another difference between gender dysphoric children and adolescents is in the sex ratios for each age group. In clinically referred, gender dysphoric children under age 12, the male/female ratio ranges from 6:1 to 3:1 (Zucker, 2004). In clinically referred, gender dysphoric adolescents older than age 12, the male/female ratio is close to 1:1 (Cohen-Kettenis & Pfäfflin, 2003).

As discussed in section IV and by Zucker and Lawrence (2009), formal epidemiologic studies on gender dysphoria – in children, adolescents, and adults – are lacking. Additional research is needed to refine estimates of its prevalence and persistence in different populations worldwide.

⁵ Gender nonconforming behaviors in children may continue into adulthood, but such behaviors are not necessarily indicative of gender dysphoria and a need for treatment. As described in section III, gender dysphoria is not synonymous with diversity in gender expression.

Phenomenology in Children

Children as young as age two may show features that could indicate gender dysphoria. They may express a wish to be of the other sex and be unhappy about their physical sex characteristics and functions. In addition, they may prefer clothes, toys, and games that are commonly associated with the other sex and prefer playing with other-sex peers. There appears to be heterogeneity in these features: Some children demonstrate extremely gender nonconforming behavior and wishes, accompanied by persistent and severe discomfort with their primary sex characteristics. In other children, these characteristics are less intense or only partially present (Cohen-Kettenis et al., 2006; Knudson, De Cuypere, & Bockting, 2010a).

It is relatively common for gender dysphoric children to have co-existing internalizing disorders such as anxiety and depression (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Wallien, Swaab, & Cohen-Kettenis, 2007; Zucker, Owen, Bradley, & Ameeriar, 2002). The prevalence of autistic spectrum disorders seems to be higher in clinically referred, gender dysphoric children than in the general population (de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010).

Phenomenology in Adolescents

In most children, gender dysphoria will disappear before or early in puberty. However, in some children these feelings will intensify and body aversion will develop or increase as they become adolescents and their secondary sex characteristics develop (Cohen-Kettenis, 2001; Cohen-Kettenis & Pfäfflin, 2003; Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Data from one study suggest that more extreme gender nonconformity in childhood is associated with persistence of gender dysphoria into late adolescence and early adulthood (Wallien & Cohen-Kettenis, 2008). Yet many adolescents and adults presenting with gender dysphoria do not report a history of childhood gender nonconforming behaviors (Docter, 1988; Landén, Wålinder, & Lundström, 1998). Therefore, it may come as a surprise to others (parents, other family members, friends, and community members) when a youth's gender dysphoria first becomes evident in adolescence.

Adolescents who experience their primary and/or secondary sex characteristics and their sex assigned at birth as inconsistent with their gender identity may be intensely distressed about it. Many, but not all, gender dysphoric adolescents have a strong wish for hormones and surgery. Increasing numbers of adolescents have already started living in their desired gender role upon entering high school (Cohen-Kettenis & Pfäfflin, 2003).

Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment – starting with GnRH analogues to suppress puberty in the first Tanner stages – differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., in press). The percentages of treated adolescents are likely influenced by the organization of health care, insurance aspects, cultural differences, opinions of health professionals, and diagnostic procedures offered in different settings.

Inexperienced clinicians may mistake indications of gender dysphoria for delusions. Phenomenologically, there is a qualitative difference between the presentation of gender dysphoria and the presentation of delusions or other psychotic symptoms. The vast majority of children and adolescents with gender dysphoria are not suffering from underlying severe psychiatric illness such as psychotic disorders (Steensma, Biemond, de Boer, & Cohen-Kettenis, published online ahead of print January 7, 2011).

It is more common for adolescents with gender dysphoria to have co-existing internalizing disorders such as anxiety and depression, and/or externalizing disorders such as oppositional defiant disorder (de Vries et al., 2010). As in children, there seems to be a higher prevalence of autistic spectrum disorders in clinically referred, gender dysphoric adolescents than in the general adolescent population (de Vries et al., 2010).

Competency of Mental Health Professionals Working with Children or Adolescents with Gender Dysphoria

The following are recommended minimum credentials for mental health professionals who assess, refer, and offer therapy to children and adolescents presenting with gender dysphoria:

1. Meet the competency requirements for mental health professionals working with adults, as outlined in section VII;
2. Trained in childhood and adolescent developmental psychopathology;
3. Competent in diagnosing and treating the ordinary problems of children and adolescents.

Roles of Mental Health Professionals Working with Children and Adolescents with Gender Dysphoria

The roles of mental health professionals working with gender dysphoric children and adolescents may include the following:

1. Directly assess gender dysphoria in children and adolescents (see general guidelines for assessment, below).
2. Provide family counseling and supportive psychotherapy to assist children and adolescents with exploring their gender identity, alleviating distress related to their gender dysphoria, and ameliorating any other psychosocial difficulties.
3. Assess and treat any co-existing mental health concerns of children or adolescents (or refer to another mental health professional for treatment). Such concerns should be addressed as part of the overall treatment plan.
4. Refer adolescents for additional physical interventions (such as puberty suppressing hormones) to alleviate gender dysphoria. The referral should include documentation of an assessment of gender dysphoria and mental health, the adolescent's eligibility for physical interventions (outlined below), the mental health professional's relevant expertise, and any other information pertinent to the youth's health and referral for specific treatments.
5. Educate and advocate on behalf of gender dysphoric children, adolescents, and their families in their community (e.g., day care centers, schools, camps, other organizations). This is particularly important in light of evidence that children and adolescents who do not conform to socially prescribed gender norms may experience harassment in school (Grossman, D'Augelli, & Salter, 2006; Grossman, D'Augelli, Howell, & Hubbard, 2006; Sausa, 2005), putting them at risk for social isolation, depression, and other negative sequelae (Nuttbrock et al., 2010).
6. Provide children, youth, and their families with information and referral for peer support, such as support groups for parents of gender nonconforming and transgender children (Gold & MacNish, 2011; Pleak, 1999; Rosenberg, 2002).

Assessment and psychosocial interventions for children and adolescents are often provided within a multi-disciplinary gender identity specialty service. If such a multidisciplinary service is not available, a mental health professional should provide consultation and liaison arrangements with a pediatric endocrinologist for the purpose of assessment, education, and involvement in any decisions about physical interventions.

Psychological Assessment of Children and Adolescents

When assessing children and adolescents who present with gender dysphoria, mental health professionals should broadly conform to the following guidelines:

1. Mental health professionals should not dismiss or express a negative attitude towards nonconforming gender identities or indications of gender dysphoria. Rather, they should acknowledge the presenting concerns of children, adolescents, and their families; offer a thorough assessment for gender dysphoria and any co-existing mental health concerns; and educate clients and their families about therapeutic options, if needed. Acceptance and removal of secrecy can bring considerable relief to gender dysphoric children/adolescents and their families.
2. Assessment of gender dysphoria and mental health should explore the nature and characteristics of a child's or adolescent's gender identity. A psychodiagnostic and psychiatric assessment – covering the areas of emotional functioning, peer and other social relationships, and intellectual functioning/school achievement – should be performed. Assessment should include an evaluation of the strengths and weaknesses of family functioning. Emotional and behavioral problems are relatively common, and unresolved issues in a child's or youth's environment may be present (de Vries, Doreleijers, Steensma, & Cohen-Kettenis, 2011; Di Ceglie & Thümmel, 2006; Wallien et al., 2007).
3. For adolescents, the assessment phase should also be used to inform youth and their families about the possibilities and limitations of different treatments. This is necessary for informed consent, but also important for assessment. The way that adolescents respond to information about the reality of sex reassignment can be diagnostically informative. Correct information may alter a youth's desire for certain treatment, if the desire was based on unrealistic expectations of its possibilities.

Psychological and Social Interventions for Children and Adolescents

When supporting and treating children and adolescents with gender dysphoria, health professionals should broadly conform to the following guidelines:

1. Mental health professionals should help families to have an accepting and nurturing response to the concerns of their gender dysphoric child or adolescent. Families play an important role in the psychological health and well-being of youth (Brill & Pepper, 2008; Lev, 2004). This also applies to peers and mentors from the community, who can be another source of social support.

2. Psychotherapy should focus on reducing a child's or adolescent's distress related to the gender dysphoria and on ameliorating any other psychosocial difficulties. For youth pursuing sex reassignment, psychotherapy may focus on supporting them before, during, and after reassignment. Formal evaluations of different psychotherapeutic approaches for this situation have not been published, but several counseling methods have been described (Cohen-Kettenis, 2006; de Vries, Cohen-Kettenis, & Delemarre-van de Waal, 2006; Di Ceglie & Thümmel, 2006; Hill, Menvielle, Sica, & Johnson, 2010; Malpas, in press; Menvielle & Tuerk, 2002; Rosenberg, 2002; Vanderburgh, 2009; Zucker, 2006).

Treatment aimed at trying to change a person's gender identity and expression to become more congruent with sex assigned at birth has been attempted in the past without success (Gelder & Marks, 1969; Greenson, 1964), particularly in the long term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

1. Families should be supported in managing uncertainty and anxiety about their child's or adolescent's psychosexual outcomes and in helping youth to develop a positive self-concept.
2. Mental health professionals should not impose a binary view of gender. They should give ample room for clients to explore different options for gender expression. Hormonal or surgical interventions are appropriate for some adolescents, but not for others.
3. Clients and their families should be supported in making difficult decisions regarding the extent to which clients are allowed to express a gender role that is consistent with their gender identity, as well as the timing of changes in gender role and possible social transition. For example, a client might attend school while undergoing social transition only partly (e.g., by wearing clothing and having a hairstyle that reflects gender identity) or completely (e.g., by also using a name and pronouns congruent with gender identity). Difficult issues include whether and when to inform other people of the client's situation, and how others in their lives should respond.
4. Health professionals should support clients and their families as educators and advocates in their interactions with community members and authorities such as teachers, school boards, and courts.
5. Mental health professionals should strive to maintain a therapeutic relationship with gender nonconforming children/adolescents and their families throughout any subsequent social changes or physical interventions. This ensures that decisions about gender expression and the treatment of gender dysphoria are thoughtfully and recurrently considered. The same reasoning applies if a child or adolescent has already socially changed gender role prior to being seen by a mental health professional.

Social Transition in Early Childhood

Some children state that they want to make a social transition to a different gender role long before puberty. For some children, this may reflect an expression of their gender identity. For others, this could be motivated by other forces. Families vary in the extent to which they allow their young children to make a social transition to another gender role. Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood. Outcomes research with children who completed early social transitions would greatly inform future clinical recommendations.

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children. They should provide information and help parents to weigh the potential benefits and challenges of particular choices. Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria (Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008). A change back to the original gender role can be highly distressing and even result in postponement of this second social transition on the child's part (Steensma & Cohen-Kettenis, 2011). For reasons such as these, parents may want to present this role change as an exploration of living in another gender role, rather than an irreversible situation. Mental health professionals can assist parents in identifying potential in-between solutions or compromises (e.g., only when on vacation). It is also important that parents explicitly let the child know that there is a way back.

Regardless of a family's decisions regarding transition (timing, extent), professionals should counsel and support them as they work through the options and implications. If parents do not allow their young child to make a gender role transition, they may need counseling to assist them with meeting their child's needs in a sensitive and nurturing way, ensuring that the child has ample possibilities to explore gender feelings and behavior in a safe environment. If parents do allow their young child to make a gender role transition, they may need counseling to facilitate a positive experience for their child. For example, they may need support in using correct pronouns, maintaining a safe and supportive environment for their transitioning child (e.g., in school, peer group settings), and communicating with other people in their child's life. In either case, as a child nears puberty, further assessment may be needed as options for physical interventions become relevant.

Physical Interventions for Adolescents

Before any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken, as outlined above. The duration of this exploration may vary considerably depending on the complexity of the situation.

Physical interventions should be addressed in the context of adolescent development. Some identity beliefs in adolescents may become firmly held and strongly expressed, giving a false impression of irreversibility. An adolescent's shift towards gender conformity can occur primarily to please the parents and may not persist or reflect a permanent change in gender dysphoria (Hembree et al., 2009; Steensma et al., published online ahead of print January 7, 2011).

Physical interventions for adolescents fall into three categories or stages (Hembree et al., 2009):

1. *Fully reversible interventions.* These involve the use of GnRH analogues to suppress estrogen or testosterone production and consequently delay the physical changes of puberty. Alternative treatment options include progestins (most commonly medroxyprogesterone) or other medications (such as spironolactone) that decrease the effects of androgens secreted by the testicles of adolescents who are not receiving GnRH analogues. Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses.
2. *Partially reversible interventions.* These include hormone therapy to masculinize or feminize the body. Some hormone-induced changes may need reconstructive surgery to reverse the effect (e.g., gynaecomastia caused by estrogens), while other changes are not reversible (e.g., deepening of the voice caused by testosterone).
3. *Irreversible interventions.* These are surgical procedures.

A staged process is recommended to keep options open through the first two stages. Moving from one stage to another should not occur until there has been adequate time for adolescents and their parents to assimilate fully the effects of earlier interventions.

Fully Reversible Interventions

Adolescents may be eligible for puberty suppressing hormones as soon as pubertal changes have begun. In order for adolescents and their parents to make an informed decision about pubertal delay, it is recommended that adolescents experience the onset of puberty to at least Tanner Stage 2. Some children may arrive at this stage at very young ages (e.g., 9 years of age). Studies

evaluating this approach only included children who were at least 12 years of age (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011; de Vries, Steensma et al., 2010; Delemarre-van de Waal, van Weissenbruch, & Cohen Kettenis, 2004; Delemarre-van de Waal & Cohen-Kettenis, 2006).

Two goals justify intervention with puberty suppressing hormones: (i) their use gives adolescents more time to explore their gender nonconformity and other developmental issues; and (ii) their use may facilitate transition by preventing the development of sex characteristics that are difficult or impossible to reverse if adolescents continue on to pursue sex reassignment.

Puberty suppression may continue for a few years, at which time a decision is made to either discontinue all hormone therapy or transition to a feminizing/masculinizing hormone regimen. Pubertal suppression does not inevitably lead to social transition or to sex reassignment.

Criteria for puberty suppressing hormones

In order for adolescents to receive puberty suppressing hormones, the following minimum criteria must be met:

1. The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
2. Gender dysphoria emerged or worsened with the onset of puberty;
3. Any co-existing psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment;
4. The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process.

Regimens, monitoring, and risks for puberty suppression

For puberty suppression, adolescents with male genitalia should be treated with GnRH analogues, which stop luteinizing hormone secretion and therefore testosterone secretion. Alternatively, they may be treated with progestins (such as medroxyprogesterone) or with other medications that block testosterone secretion and/or neutralize testosterone action. Adolescents with female genitalia should be treated with GnRH analogues, which stop the production of estrogens and

progesterone. Alternatively, they may be treated with progestins (such as medroxyprogesterone). Continuous oral contraceptives (or depot medroxyprogesterone) may be used to suppress menses. In both groups of adolescents, use of GnRH analogues is the preferred treatment (Hembree et al., 2009), but their high cost is prohibitive for some patients

During pubertal suppression, an adolescent's physical development should be carefully monitored – preferably by a pediatric endocrinologist – so that any necessary interventions can occur (e.g., to establish an adequate gender appropriate height, to improve iatrogenic low bone marrow density) (Hembree et al., 2009).

Early use of puberty suppressing hormones may avert negative social and emotional consequences of gender dysphoria more effectively than their later use would. Intervention in early adolescence should be managed with pediatric endocrinological advice, when available. Adolescents with male genitalia who start GnRH analogues early in puberty should be informed that this could result in insufficient penile tissue for penile inversion vaginoplasty techniques (alternative techniques, such as the use of a skin graft or colon tissue, are available).

Neither puberty suppression nor allowing puberty to occur is a neutral act. On the one hand, functioning in later life can be compromised by the development of irreversible secondary sex characteristics during puberty and by years spent experiencing intense gender dysphoria. On the other hand, there are concerns about negative physical side effects of GnRH analog use (e.g., on bone development and height). Although the very first results of this approach (as assessed for adolescents followed over 10 years) are promising (Cohen-Kettenis et al., 2011; Delemarre-van de Waal & Cohen-Kettenis, 2006), the long-term effects can only be determined when the earliest treated patients reach the appropriate age.

Partially Reversible Interventions

Adolescents may be eligible to begin feminizing/masculinizing hormone therapy, preferably with parental consent. In many countries, 16-year-olds are legal adults for medical decision-making and do not require parental consent. Ideally, treatment decisions should be made among the adolescent, the family, and the treatment team.

Regimens for hormone therapy in gender dysphoric adolescents differ substantially from those used in adults (Hembree et al., 2009). The hormone regimens for youth are adapted to account for the somatic, emotional, and mental development that occurs throughout adolescence (Hembree et al., 2009).

Irreversible Interventions

Genital surgery should not be carried out until (i) patients reach the legal age of majority in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention.

Chest surgery in FtM patients could be carried out earlier, preferably after ample time of living in the desired gender role and after one year of testosterone treatment. The intent of this suggested sequence is to give adolescents sufficient opportunity to experience and socially adjust in a more masculine gender role, before undergoing irreversible surgery. However, different approaches may be more suitable, depending on an adolescent's specific clinical situation and goals for gender identity expression.

Risks of Withholding Medical Treatment for Adolescents

Refusing timely medical interventions for adolescents might prolong gender dysphoria and contribute to an appearance that could provoke abuse and stigmatization. As the level of gender-related abuse is strongly associated with the degree of psychiatric distress during adolescence (Nuttbrock et al., 2010), withholding puberty suppression and subsequent feminizing or masculinizing hormone therapy is not a neutral option for adolescents.

VII

Mental Health

Transsexual, transgender, and gender nonconforming people might seek the assistance of a mental health professional for any number of reasons. Regardless of a person's reason for seeking care, mental health professionals should have familiarity with gender nonconformity, act with appropriate cultural competence, and exhibit sensitivity in providing care.

This section of the SOC focuses on the role of mental health professionals in the care of adults seeking help for gender dysphoria and related concerns. Professionals working with gender dysphoric children, adolescents, and their families should consult section VI.

Competency of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

The training of mental health professionals competent to work with gender dysphoric adults rests upon basic general clinical competence in the assessment, diagnosis, and treatment of mental health concerns. Clinical training may occur within any discipline that prepares mental health professionals for clinical practice, such as psychology, psychiatry, social work, mental health counseling, marriage and family therapy, nursing, or family medicine with specific training in behavioral health and counseling. The following are recommended minimum credentials for mental health professionals who work with adults presenting with gender dysphoria:

1. A master's degree or its equivalent in a clinical behavioral science field. This degree or a more advanced one should be granted by an institution accredited by the appropriate national or regional accrediting board. The mental health professional should have documented credentials from a relevant licensing board or equivalent for that country.
2. Competence in using the *Diagnostic Statistical Manual of Mental Disorders* and/or the *International Classification of Diseases* for diagnostic purposes.
3. Ability to recognize and diagnose co-existing mental health concerns and to distinguish these from gender dysphoria.
4. Documented supervised training and competence in psychotherapy or counseling.
5. Knowledgeable about gender nonconforming identities and expressions, and the assessment and treatment of gender dysphoria.
6. Continuing education in the assessment and treatment of gender dysphoria. This may include attending relevant professional meetings, workshops, or seminars; obtaining supervision from a mental health professional with relevant experience; or participating in research related to gender nonconformity and gender dysphoria.

In addition to the minimum credentials above, it is recommended that mental health professionals develop and maintain cultural competence to facilitate their work with transsexual, transgender, and gender nonconforming clients. This may involve, for example, becoming knowledgeable about current community, advocacy, and public policy issues relevant to these clients and their families. Additionally, knowledge about sexuality, sexual health concerns, and the assessment and treatment of sexual disorders is preferred.

Mental health professionals who are new to the field (irrespective of their level of training and other experience) should work under the supervision of a mental health professional with established competence in the assessment and treatment of gender dysphoria.

Tasks of Mental Health Professionals Working with Adults Who Present with Gender Dysphoria

Mental health professionals may serve transsexual, transgender, and gender nonconforming individuals and their families in many ways, depending on a client's needs. For example, mental health professionals may serve as a psychotherapist, counselor, or family therapist, or as a diagnostician/assessor, advocate, or educator.

Mental health professionals should determine a client's reasons for seeking professional assistance. For example, a client may be presenting for any combination of the following health care services: psychotherapeutic assistance to explore gender identity and expression or to facilitate a coming out process; assessment and referral for feminizing/masculinizing medical interventions; psychological support for family members (partners, children, extended family); or psychotherapy unrelated to gender concerns or other professional services.

Below are general guidelines for common tasks that mental health professionals may fulfill in working with adults who present with gender dysphoria.

Tasks Related to Assessment and Referral

1. Assess gender dysphoria

Mental health professionals assess clients' gender dysphoria in the context of an evaluation of their psychosocial adjustment (Bockting et al., 2006; Lev, 2004, 2009). The evaluation includes, at a minimum, assessment of gender identity and gender dysphoria, history and development of gender dysphoric feelings, the impact of stigma attached to gender nonconformity on mental health, and the availability of support from family, friends, and peers (for example, in person or online contact with other transsexual, transgender, or gender nonconforming individuals or groups). The evaluation may result in no diagnosis, in a formal diagnosis related to gender dysphoria, and/or in other diagnoses that describe aspects of the client's health and psychosocial adjustment. The role

of mental health professionals includes making reasonably sure that the gender dysphoria is not secondary to or better accounted for by other diagnoses.

Mental health professionals with the competencies described above (hereafter called “a qualified mental health professional”) are best prepared to conduct this assessment of gender dysphoria. However, this task may instead be conducted by another type of health professional who has appropriate training in behavioral health and is competent in the assessment of gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy. This professional may be the prescribing hormone therapy provider or a member of that provider’s health care team.

2. Provide information regarding options for gender identity and expression and possible medical interventions

An important task of mental health professionals is to educate clients regarding the diversity of gender identities and expressions and the various options available to alleviate gender dysphoria. Mental health professionals then may facilitate a process (or refer elsewhere) in which clients explore these various options, with the goals of finding a comfortable gender role and expression and becoming prepared to make a fully informed decision about available medical interventions, if needed. This process may include referral for individual, family, and group therapy and/or to community resources and avenues for peer support. The professional and the client discuss the implications, both short- and long-term, of any changes in gender role and use of medical interventions. These implications can be psychological, social, physical, sexual, occupational, financial, and legal (Bockting et al., 2006; Lev, 2004).

This task is also best conducted by a qualified mental health professional, but may be conducted by another health professional with appropriate training in behavioral health and with sufficient knowledge about gender nonconforming identities and expressions and about possible medical interventions for gender dysphoria, particularly when functioning as part of a multidisciplinary specialty team that provides access to feminizing/masculinizing hormone therapy.

3. Assess, diagnose, and discuss treatment options for co-existing mental health concerns

Clients presenting with gender dysphoria may struggle with a range of mental health concerns (Gómez-Gil, Trilla, Salamero, Godás, & Valdés, 2009; Murad et al., 2010) whether related or unrelated to what is often a long history of gender dysphoria and/or chronic minority stress. Possible concerns include anxiety, depression, self-harm, a history of abuse and neglect, compulsivity, substance abuse, sexual concerns, personality disorders, eating disorders, psychotic disorders, and autistic spectrum disorders (Bockting et al., 2006; Nuttbrock et al., 2010; Robinow, 2009). Mental health professionals should screen for these and other mental health concerns and incorporate

the identified concerns into the overall treatment plan. These concerns can be significant sources of distress and, if left untreated, can complicate the process of gender identity exploration and resolution of gender dysphoria (Bockting et al., 2006; Fraser, 2009a; Lev, 2009). Addressing these concerns can greatly facilitate the resolution of gender dysphoria, possible changes in gender role, the making of informed decisions about medical interventions, and improvements in quality of life.

Some clients may benefit from psychotropic medications to alleviate symptoms or treat co-existing mental health concerns. Mental health professionals are expected to recognize this and either provide pharmacotherapy or refer to a colleague who is qualified to do so. The presence of co-existing mental health concerns does not necessarily preclude possible changes in gender role or access to feminizing/masculinizing hormones or surgery; rather, these concerns need to be optimally managed prior to or concurrent with treatment of gender dysphoria. In addition, clients should be assessed for their ability to provide educated and informed consent for medical treatments.

Qualified mental health professionals are specifically trained to assess, diagnose, and treat (or refer to treatment for) these co-existing mental health concerns. Other health professionals with appropriate training in behavioral health, particularly when functioning as part of a multidisciplinary specialty team providing access to feminizing/masculinizing hormone therapy, may also screen for mental health concerns and, if indicated, provide referral for comprehensive assessment and treatment by a qualified mental health professional.

4. If applicable, assess eligibility, prepare, and refer for hormone therapy

The SOC provide criteria to guide decisions regarding feminizing/masculinizing hormone therapy (outlined in section VIII and Appendix C). Mental health professionals can help clients who are considering hormone therapy to be both psychologically prepared (for example, has made a fully informed decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (for example, has been evaluated by a physician to rule out or address medical contraindications to hormone use; has considered the psychosocial implications). If clients are of childbearing age, reproductive options (section IX) should be explored before initiating hormone therapy.

It is important for mental health professionals to recognize that decisions about hormones are first and foremost the client's decisions – as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for feminizing/masculinizing hormone therapy

People may approach a specialized provider in any discipline to pursue feminizing/masculinizing hormone therapy. However, transgender health care is an interdisciplinary field, and coordination of care and referral among a client's overall care team is recommended.

Hormone therapy can be initiated with a referral from a qualified mental health professional. Alternatively, a health professional who is appropriately trained in behavioral health and competent in the assessment of gender dysphoria may assess eligibility, prepare, and refer the patient for hormone therapy, particularly in the absence of significant co-existing mental health concerns and when working in the context of a multidisciplinary specialty team. The referring health professional provides documentation – in the chart and/or referral letter – of the patient's personal and treatment history, progress, and eligibility. Health professionals who recommend hormone therapy share the ethical and legal responsibility for that decision with the physician who provides the service.

The recommended content of the referral letter for feminizing/masculinizing hormone therapy is as follows:

1. The client's general identifying characteristics;
2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the referring health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for hormone therapy have been met, and a brief description of the clinical rationale for supporting the client's request for hormone therapy;
5. A statement about the fact that informed consent has been obtained from the patient;
6. A statement that the referring health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary, rather, the assessment and recommendation can be documented in the patient's chart.

5. If applicable, assess eligibility, prepare, and refer for surgery

The SOC also provide criteria to guide decisions regarding breast/chest surgery and genital surgery (outlined in section XI and Appendix C). Mental health professionals can help clients who are considering surgery to be both psychologically prepared (for example, has made a fully informed

decision with clear and realistic expectations; is ready to receive the service in line with the overall treatment plan; has included family and community as appropriate) and practically prepared (for example, has made an informed choice about a surgeon to perform the procedure; has arranged aftercare). If clients are of childbearing age, reproductive options (section IX) should be explored before undergoing genital surgery.

The SOC do not state criteria for other surgical procedures, such as feminizing or masculinizing facial surgery; however, mental health professionals can play an important role in helping their clients to make fully informed decisions about the timing and implications of such procedures in the context of the overall coming out or transition process.

It is important for mental health professionals to recognize that decisions about surgery are first and foremost a client's decisions – as are all decisions regarding healthcare. However, mental health professionals have a responsibility to encourage, guide, and assist clients with making fully informed decisions and becoming adequately prepared. To best support their clients' decisions, mental health professionals need to have functioning working relationships with their clients and sufficient information about them. Clients should receive prompt and attentive evaluation, with the goal of alleviating their gender dysphoria and providing them with appropriate medical services.

Referral for surgery

Surgical treatments for gender dysphoria can be initiated with a referral (one or two, depending on the type of surgery) from a qualified mental health professional. The mental health professional provides documentation – in the chart and/or referral letter – of the patient's personal and treatment history, progress, and eligibility. Mental health professionals who recommend surgery share the ethical and legal responsibility for that decision with the surgeon.

- One referral from a qualified mental health professional is needed for breast/chest surgery (e.g., mastectomy, chest reconstruction, or augmentation mammoplasty).
- Two referrals – from qualified mental health professionals who have independently assessed the patient – are needed for genital surgery (i.e., hysterectomy/salpingo-oophorectomy, orchiectomy, genital reconstructive surgeries). If the first referral is from the patient's psychotherapist, the second referral should be from a person who has only had an evaluative role with the patient. Two separate letters, or one letter signed by both (e.g., if practicing within the same clinic) may be sent. Each referral letter, however, is expected to cover the same topics in the areas outlined below.

The recommended content of the referral letters for surgery is as follows:

1. The client's general identifying characteristics;

2. Results of the client's psychosocial assessment, including any diagnoses;
3. The duration of the mental health professional's relationship with the client, including the type of evaluation and therapy or counseling to date;
4. An explanation that the criteria for surgery have been met, and a brief description of the clinical rationale for supporting the patient's request for surgery;
5. A statement about the fact that informed consent has been obtained from the patient;
6. A statement that the mental health professional is available for coordination of care and welcomes a phone call to establish this.

For providers working within a multidisciplinary specialty team, a letter may not be necessary, rather, the assessment and recommendation can be documented in the patient's chart.

Relationship of Mental Health Professionals with Hormone-Prescribing Physicians, Surgeons, and other Health Professionals

It is ideal for mental health professionals to perform their work and periodically discuss progress and obtain peer consultation from other professionals (both in mental health care and other health disciplines) who are competent in the assessment and treatment of gender dysphoria. The relationship among professionals involved in a client's health care should remain collaborative, with coordination and clinical dialogue taking place as needed. Open and consistent communication may be necessary for consultation, referral, and management of postoperative concerns.

Tasks Related to Psychotherapy

1. Psychotherapy is not an absolute requirement for hormone therapy and surgery

A mental health screening and/or assessment as outlined above is needed for referral to hormonal and surgical treatments for gender dysphoria. In contrast, psychotherapy – although highly recommended – is not a requirement.

The SOC do not recommend a minimum number of psychotherapy sessions prior to hormone therapy or surgery. The reasons for this are multifaceted (Lev, 2009). First, a minimum number of sessions tends to be construed as a hurdle, which discourages the genuine opportunity for personal growth. Second, mental health professionals can offer important support to clients throughout all

phases of exploration of gender identity, gender expression, and possible transition – not just prior to any possible medical interventions. Third, clients differ in their abilities to attain similar goals in a specified time period.

2. Goals of psychotherapy for adults with gender concerns

The general goal of psychotherapy is to find ways to maximize a person’s overall psychological well-being, quality of life, and self-fulfillment. Psychotherapy is not intended to alter a person’s gender identity; rather, psychotherapy can help an individual to explore gender concerns and find ways to alleviate gender dysphoria, if present (Bockting et al., 2006; Bockting & Coleman, 2007; Fraser, 2009a; Lev, 2004). Typically, the overarching treatment goal is to help transsexual, transgender, and gender nonconforming individuals achieve long-term comfort in their gender identity expression, with realistic chances for success in their relationships, education, and work. For additional details, see Fraser (Fraser, 2009c).

Therapy may consist of individual, couple, family, or group psychotherapy, the latter being particularly important to foster peer support.

3. Psychotherapy for transsexual, transgender, and gender nonconforming clients, including counseling and support for changes in gender role

Finding a comfortable gender role is, first and foremost, a psychosocial process. Psychotherapy can be invaluable in assisting transsexual, transgender, and gender nonconforming individuals with all of the following: (i) clarifying and exploring gender identity and role, (ii) addressing the impact of stigma and minority stress on one’s mental health and human development, and (iii) facilitating a coming out process (Bockting & Coleman, 2007; Devor, 2004; Lev, 2004), which for some individuals may include changes in gender role expression and the use of feminizing/masculinizing medical interventions.

Mental health professionals can provide support and promote interpersonal skills and resilience in individuals and their families as they navigate a world that often is ill prepared to accommodate and respect transgender, transsexual, and gender nonconforming people. Psychotherapy can also aid in alleviating any co-existing mental health concerns (e.g., anxiety, depression) identified during screening and assessment.

For transsexual, transgender, and gender nonconforming individuals who plan to change gender roles permanently and make a social gender role transition, mental health professionals can facilitate the development of an individualized plan with specific goals and timelines. While the experience of changing one’s gender role differs from person to person, the social aspects of the experience are usually challenging – often more so than the physical aspects. Because changing

gender role can have profound personal and social consequences, the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role.

Many transsexual, transgender, and gender nonconforming people will present for care without ever having been related to or accepted in the gender role that is most congruent with their gender identity. Mental health professionals can help these clients to explore and anticipate the implications of changes in gender role, and to pace the process of implementing these changes. Psychotherapy can provide a space for clients to begin to express themselves in ways that are congruent with their gender identity and, for some clients, overcome fear about changes in gender expression. Calculated risks can be taken outside of therapy to gain experience and build confidence in the new role. Assistance with coming out to family and community (friends, school, workplace) can be provided.

Other transsexual, transgender, and gender nonconforming individuals will present for care already having acquired experience (minimal, moderate, or extensive) living in a gender role that differs from that associated with their birth-assigned sex. Mental health professionals can help these clients to identify and work through potential challenges and foster optimal adjustment as they continue to express changes in their gender role.

4. Family therapy or support for family members

Decisions about changes in gender role and medical interventions for gender dysphoria have implications for not only clients, but also their families (Emerson & Rosenfeld, 1996; Fraser, 2009a; Lev, 2004). Mental health professionals can assist clients with making thoughtful decisions about communicating with family members and others about their gender identity and treatment decisions. Family therapy may include work with spouses or partners, as well as with children and other members of a client's extended family.

Clients may also request assistance with their relationships and sexual health. For example, they may want to explore their sexuality and intimacy related concerns.

Family therapy might be offered as part of the client's individual therapy and, if clinically appropriate, by the same provider. Alternatively, referrals can be made to other therapists with relevant expertise to work with family members, or to sources of peer support (e.g., online or offline support networks of partners or families).

5. Follow-up care throughout life

Mental health professionals may work with clients and their families at many stages of their lives. Psychotherapy may be helpful at different times and for various issues throughout the life cycle.

6. Etherapy, online counseling, or distance counseling

Online or etherapy has been shown to be particularly useful for people who have difficulty accessing competent psychotherapeutic treatment and who may experience isolation and stigma (Derrig-Palumbo & Zeine, 2005; Fenichel et al., 2004; Fraser, 2009b). By extrapolation, etherapy may be a useful modality for psychotherapy with transsexual, transgender, and gender nonconforming people. Etherapy offers opportunities for potentially enhanced, expanded, creative, and tailored delivery of services; however, as a developing modality it may also carry unexpected risk. Telemedicine guidelines are clear in some disciplines in some parts of the United States (Fraser, 2009b; Maheu, Pulier, Wilhelm, McMenamin, & Brown-Connolly, 2005) but not all; the international situation is even less defined (Maheu et al., 2005). Until sufficient evidence-based data on this use of etherapy is available, caution in its use is advised.

Mental health professionals engaging in etherapy are advised to stay current with their particular licensing board, professional association, and country's regulations, as well as the most recent literature pertaining to this rapidly evolving medium. A more thorough description of the potential uses, processes, and ethical concerns related to etherapy has been published (Fraser, 2009b).

Other Tasks of the Mental Health Professional

1. Educate and advocate on behalf of clients within their community (schools, workplaces, other organizations) and assist clients with making changes in identity documents

Transsexual, transgender, and gender nonconforming people may face challenges in their professional, educational, and other types of settings as they actualize their gender identity and expression (Lev, 2004, 2009). Mental health professionals can play an important role by educating people in these settings regarding gender nonconformity and by advocating on behalf of their clients (Currah, Juang, & Minter, 2006) (Currah & Minter, 2000). This role may involve consultation with school counselors, teachers, and administrators, human resources staff, personnel managers and employers, and representatives from other organizations and institutions. In addition, health providers may be called upon to support changes in a client's name and/or gender marker on identity documents such as passports, driver's licenses, birth certificates, and diplomas.

2. Provide information and referral for peer support

For some transsexual, transgender, and gender nonconforming people, an experience in peer support groups may be more instructive regarding options for gender expression than anything individual psychotherapy could offer (Rachlin, 2002). Both experiences are potentially valuable, and all people exploring gender issues should be encouraged to participate in community activities, if possible. Resources for peer support and information should be made available.

Culture and its Ramifications for Assessment and Psychotherapy

Health professionals work in enormously different environments across the world. Forms of distress that cause people to seek professional assistance in any culture are understood and classified by people in terms that are products of their own cultures (Frank & Frank, 1993). Cultural settings also largely determine how such conditions are understood by mental health professionals. Cultural differences related to gender identity and expression can affect patients, mental health professionals, and accepted psychotherapy practice. WPATH recognizes that the SOC have grown out of a Western tradition and may need to be adapted depending on the cultural context.

Ethical Guidelines Related to Mental Health Care

Mental health professionals need to be certified or licensed to practice in a given country according to that country's professional regulations (Fraser, 2009b; Pope & Vasquez, 2011). Professionals must adhere to the ethical codes of their professional licensing or certifying organizations in all of their work with transsexual, transgender, and gender nonconforming clients.

Treatment aimed at trying to change a person's gender identity and lived gender expression to become more congruent with sex assigned at birth has been attempted in the past (Gelder & Marks, 1969; Greenson, 1964), yet without success, particularly in the long term (Cohen-Kettenis & Kuiper, 1984; Pauly, 1965). Such treatment is no longer considered ethical.

If mental health professionals are uncomfortable with or inexperienced in working with transsexual, transgender, and gender nonconforming individuals and their families, they should refer clients to a competent provider or, at minimum, consult with an expert peer. If no local practitioners are available, consultation may be done via telehealth methods, assuming local requirements for distance consultation are met.

Issues of Access to Care

Qualified mental health professionals are not universally available; thus, access to quality care might be limited. WPATH aims to improve access and provides regular continuing education opportunities to train professionals from various disciplines to provide quality, transgender-specific health care. Providing mental health care from a distance through the use of technology may be one way to improve access (Fraser, 2009b).

In many places around the world, access to health care for transsexual, transgender, and gender nonconforming people is also limited by a lack of health insurance or other means to pay for needed care. WPATH urges health insurance companies and other third-party payers to cover the medically necessary treatment to alleviate gender dysphoria (American Medical Association, 2008; Anton, 2009; The World Professional Association for Transgender Health, 2008).

When faced with a client who is unable to access services, referral to available peer support resources (offline and online) is recommended. Finally, harm reduction approaches might be indicated to assist clients with making healthy decisions to improve their lives.

VIII

Hormone Therapy

Medical Necessity of Hormone Therapy

Feminizing/masculinizing hormone therapy – the administration of exogenous endocrine agents to induce feminizing or masculinizing changes – is a medically necessary intervention for many transsexual, transgender, and gender nonconforming individuals with gender dysphoria (Newfield, Hart, Dibble, & Kohler, 2006; Pfäfflin & Junge, 1998). Some people seek maximum feminization/masculinization, while others experience relief with an androgynous presentation resulting from hormonal minimization of existing secondary sex characteristics (Factor & Rothblum, 2008). Evidence for the psychosocial outcomes of hormone therapy is summarized in Appendix D.

Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Hormone therapy can provide significant comfort to patients who do not wish to make a social gender role transition or undergo surgery, or who are unable to do so (Meyer III, 2009).

Hormone therapy is a recommended criterion for some, but not all, surgical treatments for gender dysphoria (see section XI and Appendix C).

Criteria for Hormone Therapy

Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional, as outlined in section VII of the SOC. A referral is required from the mental health professional who performed the assessment, unless the assessment was done by a hormone provider who is also qualified in this area.

The criteria for hormone therapy are as follows:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the *Standards of Care* outlined in section VI);
4. If significant medical or mental health concerns are present, they must be reasonably well-controlled.

As noted in section VII of the SOC, the presence of co-existing mental health concerns does not necessarily preclude access to feminizing/masculinizing hormones; rather, these concerns need to be managed prior to or concurrent with treatment of gender dysphoria.

In selected circumstances, it can be acceptable practice to provide hormones to patients who have not fulfilled these criteria. Examples include facilitating the provision of monitored therapy using hormones of known quality as an alternative to illicit or unsupervised hormone use or to patients who have already established themselves in their affirmed gender and who have a history of prior hormone use. It is unethical to deny availability or eligibility for hormone therapy solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis B or C.

In rare cases, hormone therapy may be contraindicated due to serious individual health conditions. Health professionals should assist these patients with accessing non-hormonal interventions for gender dysphoria. A qualified mental health professional familiar with the patient is an excellent resource in these circumstances.

Informed Consent

Feminizing/masculinizing hormone therapy may lead to irreversible physical changes. Thus, hormone therapy should be provided only to those who are legally able to provide informed consent. This includes people who have been declared by a court to be emancipated minors, incarcerated people, and cognitively impaired people who are considered competent to participate in their medical decisions (see also Bockting et al., 2006). Providers should document in the medical record that comprehensive information has been provided and understood about all relevant aspects of the hormone therapy, including both possible benefits and risks and the impact on reproductive capacity.

Relationship between the Standards of Care and Informed Consent Model Protocols

A number of community health centers in the United States have developed protocols for providing hormone therapy based on an approach that has become known as the Informed Consent Model (Callen Lorde Community Health Center, 2000, 2011; Fenway Community Health Transgender Health Program, 2007; Tom Waddell Health Center, 2006). These protocols are consistent with the guidelines presented in the WPATH *Standards of Care, Version 7*. The SOC are flexible clinical guidelines; they allow for tailoring of interventions to the needs of the individual receiving services and for tailoring of protocols to the approach and setting in which these services are provided (Ehrbar & Gorton, 2010).

Obtaining informed consent for hormone therapy is an important task of providers to ensure that patients understand the psychological and physical benefits and risks of hormone therapy, as well as its psychosocial implications. Providers prescribing the hormones or health professionals recommending the hormones should have the knowledge and experience to assess gender dysphoria. They should inform individuals of the particular benefits, limitations, and risks of hormones, given the patient's age, previous experience with hormones, and concurrent physical or mental health concerns.

Screening for and addressing acute or current mental health concerns is an important part of the informed consent process. This may be done by a mental health professional or by an appropriately trained prescribing provider (see section VII of the SOC). The same provider or another appropriately trained member of the health care team (e.g., a nurse) can address the psychosocial implications of taking hormones when necessary (e.g., the impact of masculinization/feminization on how one is perceived and its potential impact on relationships with family, friends, and coworkers). If indicated, these providers will make referrals for psychotherapy and for the assessment and treatment of co-existing mental health concerns such as anxiety or depression.

The difference between the Informed Consent Model and *SOC, Version 7* is that the *SOC* puts greater emphasis on the important role that mental health professionals can play in alleviating gender dysphoria and facilitating changes in gender role and psychosocial adjustment. This may include a comprehensive mental health assessment and psychotherapy, when indicated. In the Informed Consent Model, the focus is on obtaining informed consent as the threshold for the initiation of hormone therapy in a multidisciplinary, harm-reduction environment. Less emphasis is placed on the provision of mental health care until the patient requests it, unless significant mental health concerns are identified that would need to be addressed before hormone prescription.

Physical Effects of Hormone Therapy

Feminizing/masculinizing hormone therapy will induce physical changes that are more congruent with a patient's gender identity.

- In FtM patients, the following physical changes are expected to occur: deepened voice, clitoral enlargement (variable), growth in facial and body hair, cessation of menses, atrophy of breast tissue, increased libido, and decreased percentage of body fat compared to muscle mass.
- In MtF patients, the following physical changes are expected to occur: breast growth (variable), decreased libido and erections, decreased testicular size, and increased percentage of body fat compared to muscle mass.

Most physical changes, whether feminizing or masculinizing, occur over the course of two years. The amount of physical change and the exact timeline of effects can be highly variable. Tables 1a and 1b outline the approximate time course of these physical changes.

TABLE 1A: EFFECTS AND EXPECTED TIME COURSE OF MASCULINIZING HORMONES ^A

Effect	Expected Onset ^B	Expected Maximum Effect ^B
Skin oiliness/acne	1-6 months	1-2 years
Facial/body hair growth	3-6 months	3-5 years
Scalp hair loss	>12 months ^C	variable
Increased muscle mass/strength	6-12 months	2-5 years ^D
Body fat redistribution	3-6 months	2-5 years
Cessation of menses	2-6 months	n/a
Clitoral enlargement	3-6 months	1-2 years
Vaginal atrophy	3-6 months	1-2 years
Deepened voice	3-12 months	1-2 years

^A Adapted with permission from Hembree et al.(2009). Copyright 2009, The Endocrine Society.

^B Estimates represent published and unpublished clinical observations.

^C Highly dependent on age and inheritance; may be minimal.

^D Significantly dependent on amount of exercise.

TABLE 1B: EFFECTS AND EXPECTED TIME COURSE OF FEMINIZING HORMONES ^A

Effect	Expected Onset ^B	Expected Maximum Effect ^B
Body fat redistribution	3-6 months	2-5 years
Decreased muscle mass/ strength	3-6 months	1-2 years ^C
Softening of skin/decreased oiliness	3-6 months	unknown
Decreased libido	1-3 months	1-2 years
Decreased spontaneous erections	1-3 months	3-6 months
Male sexual dysfunction	variable	variable
Breast growth	3-6 months	2-3 years
Decreased testicular volume	3-6 months	2-3 years
Decreased sperm production	variable	variable
Thinning and slowed growth of body and facial hair	6-12 months	> 3 years ^D
Male pattern baldness	No regrowth, loss stops 1-3 months	1-2 years

^A Adapted with permission from Hembree et al. (2009). Copyright 2009, The Endocrine Society.

^B Estimates represent published and unpublished clinical observations.

^C Significantly dependent on amount of exercise.

^D Complete removal of male facial and body hair requires electrolysis, laser treatment, or both.

The degree and rate of physical effects depends in part on the dose, route of administration, and medications used, which are selected in accordance with a patient's specific medical goals (e.g., changes in gender role expression, plans for sex reassignment) and medical risk profile. There is no current evidence that response to hormone therapy – with the possible exception of voice deepening in FtM persons – can be reliably predicted based on age, body habitus, ethnicity, or family appearance. All other factors being equal, there is no evidence to suggest that any medically approved type or method of administering hormones is more effective than any other in producing the desired physical changes.

Risks of Hormone Therapy

All medical interventions carry risks. The likelihood of a serious adverse event is dependent on numerous factors: the medication itself, dose, route of administration, and a patient's clinical characteristics (age, co-morbidities, family history, health habits). It is thus impossible to predict whether a given adverse effect will happen in an individual patient.

The risks associated with feminizing/masculinizing hormone therapy for the transsexual, transgender, and gender nonconforming population as a whole are summarized in Table 2. Based on the level of evidence, risks are categorized as follows: (i) likely increased risk with hormone therapy, (ii) possibly increased risk with hormone therapy, or (iii) inconclusive or no increased risk. Items in the last category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Additional detail about these risks can be found in Appendix B, which is based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (Dahl, Feldman, Goldberg, & Jaber, 2006; Ettner, Monstrey, & Eyler, 2007).

TABLE 2: RISKS ASSOCIATED WITH HORMONE THERAPY. BOLDED ITEMS ARE CLINICALLY SIGNIFICANT

Risk Level	Feminizing hormones	Masculinizing hormones
Likely increased risk	Venous thromboembolic disease^A Gallstones Elevated liver enzymes Weight gain Hypertriglyceridemia	Polycythemia Weight gain Acne Androgenic alopecia (balding) Sleep apnea
Likely increased risk with presence of additional risk factors ^B	Cardiovascular disease	
Possible increased risk	Hypertension Hyperprolactinemia or prolactinoma ^A	Elevated liver enzymes Hyperlipidemia
Possible increased risk with presence of additional risk factors ^B	Type 2 diabetes^A	Destabilization of certain psychiatric disorders^C Cardiovascular disease Hypertension Type 2 diabetes
No increased risk or inconclusive	Breast cancer	Loss of bone density Breast cancer Cervical cancer Ovarian cancer Uterine cancer

^A Risk is greater with oral estrogen administration than with transdermal estrogen administration.

^B Additional risk factors include age.

^C Includes bipolar, schizoaffective, and other disorders that may include manic or psychotic symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

Competency of Hormone-Prescribing Physicians, Relationship with Other Health Professionals

Feminizing/masculinizing hormone therapy is best undertaken in the context of a complete approach to health care that includes comprehensive primary care and a coordinated approach to psychosocial issues (Feldman & Safer, 2009). While psychotherapy or ongoing counseling is not required for the initiation of hormone therapy, if a therapist is involved, then regular communication among health professionals is advised (with the patient's consent) to ensure that the transition process is going well, both physically and psychosocially.

With appropriate training, feminizing/masculinizing hormone therapy can be managed by a variety of providers, including nurse practitioners and primary care physicians (Dahl et al., 2006). Medical visits relating to hormone maintenance provide an opportunity to deliver broader care to a population that is often medically underserved (Clements, Wilkinson, Kitano, & Marx, 1999; Feldman, 2007; Xavier, 2000). Many of the screening tasks and management of co-morbidities associated with long-term hormone use, such as cardiovascular risk factors and cancer screening, fall more uniformly within the scope of primary care rather than specialist care (American Academy of Family Physicians, 2005; Eyler, 2007; World Health Organization, 2008), particularly in locations where dedicated gender teams or specialized physicians are not available.

Given the multidisciplinary needs of transsexual, transgender, and gender nonconforming people seeking hormone therapy, as well as the difficulties associated with fragmentation of care in general (World Health Organization, 2008), WPATH strongly encourages the increased training and involvement of primary care providers in the area of feminizing/masculinizing hormone therapy. If hormones are prescribed by a specialist, there should be close communication with the patient's primary care provider. Conversely, an experienced hormone provider or endocrinologist should be involved if the primary care physician has no experience with this type of hormone therapy, or if the patient has a pre-existing metabolic or endocrine disorder that could be affected by endocrine therapy.

While formal training programs in transgender medicine do not yet exist, hormone providers have a responsibility to obtain appropriate knowledge and experience in this field. Clinicians can increase their experience and comfort in providing feminizing/masculinizing hormone therapy by co-managing care or consulting with a more experienced provider, or by providing more limited types of hormone therapy before progressing to initiation of hormone therapy. Because this field of medicine is evolving, clinicians should become familiar and keep current with the medical literature, and discuss emerging issues with colleagues. Such discussions might occur through networks established by WPATH and other national/local organizations.

Responsibilities of Hormone-Prescribing Physicians

In general, clinicians who prescribe hormone therapy should engage in the following tasks:

1. Perform an initial evaluation that includes discussion of a patient's physical transition goals, health history, physical examination, risk assessment, and relevant laboratory tests.
2. Discuss with patients the expected effects of feminizing/masculinizing medications and the possible adverse health effects. These effects can include a reduction in fertility (Feldman & Safer, 2009; Hembree et al., 2009). Therefore, reproductive options should be discussed with patients before starting hormone therapy (see section IX).
3. Confirm that patients have the capacity to understand the risks and benefits of treatment and are capable of making an informed decision about medical care.
4. Provide ongoing medical monitoring, including regular physical and laboratory examination to monitor hormone effectiveness and side effects.
5. Communicate as needed with a patient's primary care provider, mental health professional, and surgeon.
6. If needed, provide patients with a brief written statement indicating that they are under medical supervision and care that includes feminizing/masculinizing hormone therapy. Particularly during the early phases of hormone treatment, a patient may wish to carry this statement at all times to help prevent difficulties with the police and other authorities.

Depending on the clinical situation for providing hormones (see below), some of these responsibilities are less relevant. Thus, the degree of counseling, physical examinations, and laboratory evaluations should be individualized to a patient's needs.

Clinical Situations for Hormone Therapy

There are circumstances in which clinicians may be called upon to provide hormones without necessarily initiating or maintaining long-term feminizing/masculinizing hormone therapy. By acknowledging these different clinical situations (see below, from least to highest level of complexity), it may be possible to involve clinicians in feminizing/masculinizing hormone therapy who might not otherwise feel able to offer this treatment.

1. Bridging

Whether prescribed by another clinician or obtained through other means (e.g., purchased over the internet), patients may present for care already on hormone therapy. Clinicians can provide a limited (1-6 month) prescription for hormones while helping patients find a provider who can prescribe long-term hormone therapy. Providers should assess a patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated (Dahl et al., 2006; Feldman & Safer, 2009). If hormones were previously prescribed, medical records should be requested (with the patient's permission) to obtain the results of baseline examinations and laboratory tests and any adverse events. Hormone providers should also communicate with any mental health professional who is currently involved in a patient's care. If a patient has never had a psychosocial assessment as recommended by the SOC (see section VII), clinicians should refer the patient to a qualified mental health professional if appropriate and feasible (Feldman & Safer, 2009). Providers who prescribe bridging hormones need to work with patients to establish limits as to the duration of bridging therapy.

2. Hormone therapy following gonad removal

Hormone replacement with estrogen or testosterone is usually continued lifelong after an oophorectomy or orchiectomy, unless medical contraindications arise. Because hormone doses are often decreased after these surgeries (Basson, 2001; Levy, Crown, & Reid, 2003; Moore, Wisniewski, & Dobs, 2003) and only adjusted for age and co-morbid health concerns, hormone management in this situation is quite similar to hormone replacement in any hypogonadal patient.

3. Hormone maintenance prior to gonad removal

Once patients have achieved maximal feminizing/masculinizing benefits from hormones (typically two or more years), they remain on a maintenance dose. The maintenance dose is then adjusted for changes in health conditions, aging, or other considerations such as lifestyle changes (Dahl et al., 2006). When a patient on maintenance hormones presents for care, the provider should assess the patient's current regimen for safety and drug interactions and substitute safer medications or doses when indicated. The patient should continue to be monitored by physical examinations and laboratory testing on a regular basis, as outlined in the literature (Feldman & Safer, 2009; Hembree et al., 2009). The dose and form of hormones should be revisited regularly with any changes in the patient's health status and available evidence on the potential long-term risks of hormones (See *Hormone Regimens*, below).

4. Initiating hormonal feminization/masculinization

This clinical situation requires the greatest commitment in terms of provider time and expertise. Hormone therapy must be individualized based on a patient's goals, the risk/benefit ratio of medications, the presence of other medical conditions, and consideration of social and economic issues. Although a wide variety of hormone regimens have been published (Dahl et al., 2006; Hembree et al., 2009; Moore et al., 2003), there are no published reports of randomized clinical trials comparing safety and efficacy. Despite this variation, a reasonable framework for initial risk assessment and ongoing monitoring of hormone therapy can be constructed, based on the efficacy and safety evidence presented above.

Risk Assessment and Modification for Initiating Hormone Therapy

The initial evaluation for hormone therapy assesses a patient's clinical goals and risk factors for hormone-related adverse events. During the risk assessment, the patient and clinician should develop a plan for reducing risks wherever possible, either prior to initiating therapy or as part of ongoing harm reduction.

All assessments should include a thorough physical exam, including weight, height, and blood pressure. The need for breast, genital, and rectal exams, which are sensitive issues for most transsexual, transgender, and gender nonconforming patients, should be based on individual risks and preventive health care needs (Feldman & Goldberg, 2006; Feldman, 2007).

Preventive care

Hormone providers should address preventive health care with patients, particularly if a patient does not have a primary care provider. Depending on a patient's age and risk profile, there may be appropriate screening tests or exams for conditions affected by hormone therapy. Ideally, these screening tests should be carried out prior to the start of hormone therapy.

Risk assessment and modification for feminizing hormone therapy (MtF)

There are no absolute contraindications to feminizing therapy *per se*, but absolute contraindications exist for the different feminizing agents, particularly estrogen. These include previous venous thrombotic events related to an underlying hypercoagulable condition, history of estrogen-sensitive neoplasm, and end-stage chronic liver disease (Gharib et al., 2005).

Other medical conditions, as noted in Table 2 and Appendix B, can be exacerbated by estrogen or androgen blockade, and therefore should be evaluated and reasonably well controlled prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Clinicians should particularly attend to tobacco use, as it is associated with increased risk of venous thrombosis, which is further increased with estrogen use. Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of feminizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Risk assessment and modification for masculinizing hormone therapy (FtM)

Absolute contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and untreated polycythemia with a hematocrit of 55% or higher (Carnegie, 2004). Because the aromatization of testosterone to estrogen may increase risk in patients with a history of breast or other estrogen dependent cancers (Moore et al., 2003), consultation with an oncologist may be indicated prior to hormone use. Co-morbid conditions likely to be exacerbated by testosterone use should be evaluated and treated, ideally prior to starting hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009). Consultation with a cardiologist may be advisable for patients with known cardio- or cerebrovascular disease.

An increased prevalence of polycystic ovarian syndrome (PCOS) has been noted among FtM patients even in the absence of testosterone use (Baba et al., 2007; Balen, Schachter, Montgomery, Reid, & Jacobs, 1993; Bosinski et al., 1997). While there is no evidence that PCOS is related to the development of a transsexual, transgender, or gender nonconforming identity, PCOS is associated with increased risk of diabetes, cardiac disease, high blood pressure, and ovarian and endometrial cancers (Catrall & Healy, 2004). Signs and symptoms of PCOS should be evaluated prior to initiating testosterone therapy, as testosterone may affect many of these conditions. Testosterone can affect the developing fetus (Physicians' Desk Reference, 2011), and patients at risk of becoming pregnant require highly effective birth control.

Baseline laboratory values are important to both assess initial risk and evaluate possible future adverse events. Initial labs should be based on the risks of masculinizing hormone therapy outlined in Table 2, as well as individual patient risk factors, including family history. Suggested initial lab panels have been published (Feldman & Safer, 2009; Hembree et al., 2009). These can be modified for patients or health care systems with limited resources, and in otherwise healthy patients.

Clinical Monitoring during Hormone Therapy for Efficacy and Adverse Events

The purpose of clinical monitoring during hormone use is to assess the degree of feminization/masculinization and the possible presence of adverse effects of medication. However, as with the monitoring of any long-term medication, monitoring should take place in the context of comprehensive health care. Suggested clinical monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009). Patients with co-morbid medical conditions may need to be monitored more frequently. Healthy patients in geographically remote or resource-poor areas may be able to use alternative strategies, such as telehealth, or cooperation with local providers such as nurses and physician assistants. In the absence of other indications, health professionals may prioritize monitoring for those risks that are either likely to be increased by hormone therapy or possibly increased by hormone therapy but clinically serious in nature.

Efficacy and risk monitoring during feminizing hormone therapy (MtF)

The best assessment of hormone efficacy is clinical response: Is a patient developing a feminized body while minimizing masculine characteristics, consistent with that patient's gender goals? In order to more rapidly predict the hormone dosages that will achieve clinical response, one can measure testosterone levels for suppression below the upper limit of the normal female range, and estradiol levels within a premenopausal female range but well below supraphysiologic levels (Feldman & Safer, 2009; Hembree et al., 2009).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs of cardiovascular impairment and venous thromboembolism (VTE) through measurement of blood pressure, weight, and pulse; heart and lung exams; and examination of the extremities for peripheral edema, localized swelling, or pain (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual co-morbidities and risk factors, and the specific hormone regimen itself. Specific lab monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Efficacy and risk monitoring during masculinizing hormone therapy (FtM)

The best assessment of hormone efficacy is clinical response: Is a patient developing a masculinized body while minimizing feminine characteristics, consistent with that patient's gender goals? Clinicians can achieve a good clinical response with the least likelihood of adverse events by maintaining testosterone levels within the normal male range while avoiding supraphysiological

levels (Dahl et al., 2006; Hembree et al., 2009). For patients using intramuscular (IM) testosterone cypionate or enanthate, some clinicians check trough levels while others prefer midcycle levels (Dahl et al., 2006; Hembree et al., 2009; Tangpricha, Turner, Malabanan, & Holick, 2001; Tangpricha, Ducharme, Barber, & Chipkin, 2003).

Monitoring for adverse events should include both clinical and laboratory evaluation. Follow-up should include careful assessment for signs and symptoms of excessive weight gain, acne, uterine break-through bleeding, and cardiovascular impairment, as well as psychiatric symptoms in at-risk patients. Physical examinations should include measurement of pressure, weight, pulse, and skin; and heart and lung exams (Feldman & Safer, 2009). Laboratory monitoring should be based on the risks of hormone therapy described above, a patient's individual co-morbidities and risk factors, and the specific hormone regimen itself. Specific lab monitoring protocols have been published (Feldman & Safer, 2009; Hembree et al., 2009).

Hormone Regimens

To date, no controlled clinical trials of any feminizing/masculinizing hormone regimen have been conducted to evaluate safety or efficacy in producing physical transition. As a result, wide variation in doses and types of hormones have been published in the medical literature (Moore et al., 2003; Tangpricha et al., 2003; van Kesteren, Asscheman, Megens, & Gooren, 1997). In addition, access to particular medications may be limited by a patient's geographical location and/or social or economic situations. For these reasons, WPATH does not describe or endorse a particular feminizing/masculinizing hormone regimen. Rather, the medication classes and routes of administration used in most published regimens are broadly reviewed.

As outlined above, there are demonstrated safety differences in individual elements of various regimens. The Endocrine Society Guidelines (Hembree et al., 2009) and Feldman and Safer (2009) provide specific guidance regarding the types of hormones and suggested dosing to maintain levels within physiologic ranges for a patient's desired gender expression (based on goals of full feminization/masculinization). It is strongly recommend that hormone providers regularly review the literature for new information and use those medications that safely meet individual patient needs with available local resources.

Regimens for feminizing hormone therapy (MtF)

Estrogen

Use of oral estrogen, and specifically ethinyl estradiol, appears to increase the risk of VTE. Because of this safety concern, ethinyl estradiol is not recommended for feminizing hormone therapy. Transdermal estrogen is recommended for those patients with risks factors for VTE. The risk of adverse events increases with higher doses, particular those resulting in supraphysiologic levels (Hembree et al., 2009). Patients with co-morbid conditions that can be affected by estrogen should avoid oral estrogen if possible and be started at lower levels. Some patients may not be able to safely use the levels of estrogen needed to get the desired results. This possibility needs to be discussed with patients well in advance of starting hormone therapy.

Androgen reducing medications (“anti-androgens”)

A combination of estrogen and “anti-androgens” is the most commonly studied regimen for feminization. Androgen reducing medications, from a variety of classes of drugs, have the effect of reducing either endogenous testosterone levels or testosterone activity, and thus diminishing masculine characteristics such as body hair. They minimize the dosage of estrogen needed to suppress testosterone, thereby reducing the risks associated with high-dose exogenous estrogen (Prior, Vigna, Watson, Diewold, & Robinow, 1986; Prior, Vigna, & Watson, 1989).

Common anti-androgens include the following:

- Spironolactone, an antihypertensive agent, directly inhibits testosterone secretion and androgen binding to the androgen receptor. Blood pressure and electrolytes need to be monitored because of the potential for hyperkalemia.
- Cyproterone acetate is a progestational compound with anti-androgenic properties. This medication is not approved in the United States because of concerns over potential hepatotoxicity, but it is widely used elsewhere (De Cuypere et al., 2005).
- GnRH agonists (e.g., goserelin, buserelin, triptorelin) are neurohormones that block the gonadotropin releasing hormone receptor, thus blocking the release of follicle stimulating hormone and luteinizing hormone. This leads to highly effective gonadal blockade. However, these medications are expensive and only available as injectables or implants.
- 5-alpha reductase inhibitors (finasteride and dutasteride) block the conversion of testosterone to the more active agent, 5-alpha-dihydrotestosterone. These medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency.

Cyproterone and spironolactone are the most commonly used anti-androgens and are likely the most cost-effective.

Progestins

With the exception of cyproterone, the inclusion of progestins in feminizing hormone therapy is controversial (Oriel, 2000). Because progestins play a role in mammary development on a cellular level, some clinicians believe that these agents are necessary for full breast development (Basson & Prior, 1998; Oriel, 2000). However, a clinical comparison of feminization regimens with and without progestins found that the addition of progestins neither enhanced breast growth nor lowered serum levels of free testosterone (Meyer III et al., 1986). There are concerns regarding potential adverse effects of progestins, including depression, weight gain, and lipid changes (Meyer III et al., 1986; Tangpricha et al., 2003). Progestins (especially medroxyprogesterone) are also suspected to increase breast cancer risk and cardiovascular risk in women (Rossouw et al., 2002). Micronized progesterone may be better tolerated and have a more favorable impact on the lipid profile than medroxyprogesterone does (de Lignières, 1999; Fitzpatrick, Pace, & Wiita, 2000).

Regimens for masculinizing hormone therapy (FtM)

Testosterone

Testosterone generally can be given orally, transdermally, or parenterally (IM), although buccal and implantable preparations are also available. Oral testosterone undecanoate, available outside the United States, results in lower serum testosterone levels than non-oral preparations and has limited efficacy in suppressing menses (Feldman, 2005, April; Moore et al., 2003). Because intramuscular testosterone cypionate or enanthate are often administered every 2-4 weeks, some patients may notice cyclic variation in effects (e.g., fatigue and irritability at the end of the injection cycle, aggression or expansive mood at the beginning of the injection cycle), as well as more time outside the normal physiologic levels (Jockenhövel, 2004). This may be mitigated by using a lower but more frequent dosage schedule or by using a daily transdermal preparation (Dobs et al., 1999; Jockenhövel, 2004; Nieschlag et al., 2004). Intramuscular testosterone undecanoate (not currently available in the United States) maintains stable, physiologic testosterone levels over approximately 12 weeks and has been effective in both the setting of hypogonadism and in FtM individuals (Mueller, Kiesewetter, Binder, Beckmann, & Dittrich, 2007; Zitzmann, Saad, & Nieschlag, 2006). There is evidence that transdermal and intramuscular testosterone achieve similar masculinizing results, although the timeframe may be somewhat slower with transdermal preparations (Feldman, 2005, April). Especially as patients age, the goal is to use the lowest dose needed to maintain the desired clinical result, with appropriate precautions being made to maintain bone density.

Other agents

Progestins, most commonly medroxyprogesterone, can be used for a short period of time to assist with menstrual cessation early in hormone therapy. GnRH agonists can be used similarly, as well as for refractory uterine bleeding in patients without an underlying gynecological abnormality.

Bioidentical and compounded hormones

As discussion surrounding the use of bioidentical hormones in postmenopausal hormone replacement has heightened, interest has also increased in the use of similar compounds in feminizing/masculinizing hormone therapy. There is no evidence that custom compounded bioidentical hormones are safer or more effective than government agency-approved bioidentical hormones (Sood, Shuster, Smith, Vincent, & Jatoi, 2011). Therefore, it has been advised by the North American Menopause Society (2010) and others to assume that, whether the hormone is from a compounding pharmacy or not, if the active ingredients are similar, it should have a similar side-effect profile. WPATH concurs with this assessment.

IX

Reproductive Health

Many transgender, transsexual, and gender nonconforming people will want to have children. Because feminizing/masculinizing hormone therapy limits fertility (Darney, 2008; Zhang, Gu, Wang, Cui, & Bremner, 1999), it is desirable for patients to make decisions concerning fertility before starting hormone therapy or undergoing surgery to remove/alter their reproductive organs. Cases are known of people who received hormone therapy and genital surgery and later regretted their inability to parent genetically related children (De Sutter, Kira, Verschoor, & Hotimsky, 2002).

Health care professionals – including mental health professionals recommending hormone therapy or surgery, hormone-prescribing physicians, and surgeons – should discuss reproductive options with patients prior to initiation of these medical treatments for gender dysphoria. These discussions should occur even if patients are not interested in these issues at the time of treatment, which may be more common for younger patients (De Sutter, 2009). Early discussions are desirable, but not always possible. If an individual has not had complete sex reassignment surgery, it may be possible to stop hormones long enough for natal hormones to recover, allowing the production of mature

gametes (Payer, Meyer III, & Walker, 1979; Van den Broecke, Van der Elst, Liu, Hovatta, & Dhont, 2001).

Besides debate and opinion papers, very few research papers have been published on the reproductive health issues of individuals receiving different medical treatments for gender dysphoria. Another group who faces the need to preserve reproductive function in light of loss or damage to their gonads are people with malignancies that require removal of reproductive organs or use of damaging radiation or chemotherapy. Lessons learned from that group can be applied to people treated for gender dysphoria.

MtF patients, especially those who have not already reproduced, should be informed about sperm preservation options and encouraged to consider banking their sperm prior to hormone therapy. In a study examining testes that were exposed to high-dose estrogen (Payer et al., 1979), findings suggest that stopping estrogen may allow the testes to recover. In an article reporting on the opinions of MtF individuals towards sperm freezing (De Sutter et al., 2002), the vast majority of 121 survey respondents felt that the availability of freezing sperm should be discussed and offered by the medical world. Sperm should be collected before hormone therapy or after stopping the therapy until the sperm count rises again. Cryopreservation should be discussed even if there is poor semen quality. In adults with azoospermia, a testicular biopsy with subsequent cryopreservation of biopsied material for sperm is possible, but may not be successful.

Reproductive options for FtM patients might include oocyte (egg) or embryo freezing. The frozen gametes and embryo could later be used with a surrogate woman to carry to pregnancy. Studies of women with polycystic ovarian disease suggest that the ovary can recover in part from the effects of high testosterone levels (Hunter & Sterrett, 2000). Stopping the testosterone briefly might allow for ovaries to recover enough to make eggs; success likely depends on the patient's age and duration of testosterone treatment. While not systematically studied, some FtM individuals are doing exactly that, and some have been able to become pregnant and deliver children (More, 1998).

Patients should be advised that these techniques are not available everywhere and can be very costly. Transsexual, transgender, and gender nonconforming people should not be refused reproductive options for any reason.

A special group of individuals are prepubertal or pubertal adolescents who will never develop reproductive function in their natal sex due to blockers or cross gender hormones. At this time there is no technique for preserving function from the gonads of these individuals.



Voice and Communication Therapy

Communication, both verbal and nonverbal, is an important aspect of human behavior and gender expression. Transsexual, transgender, and gender nonconforming people might seek the assistance of a voice and communication specialist to develop vocal characteristics (e.g., pitch, intonation, resonance, speech rate, phrasing patterns) and non-verbal communication patterns (e.g., gestures, posture/movement, facial expressions) that facilitate comfort with their gender identity. Voice and communication therapy may help to alleviate gender dysphoria and be a positive and motivating step towards achieving one's goals for gender role expression.

Competency of Voice and Communication Specialists Working with Transsexual, Transgender, and Gender Nonconforming Clients

Specialists may include speech-language pathologists, speech therapists, and speech-voice clinicians. In most countries the professional association for speech-language pathologists requires specific qualifications and credentials for membership. In some countries the government regulates practice through licensing, certification, or registration processes (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia; Vancouver Coastal Health, Vancouver, British Columbia, Canada).

The following are recommended minimum credentials for voice and communication specialists working with transsexual, transgender, and gender nonconforming clients:

1. Specialized training and competence in the assessment and development of communication skills in transsexual, transgender, and gender nonconforming clients.
2. A basic understanding of transgender health, including hormonal and surgical treatments for feminization/masculinization and trans-specific psychosocial issues as outlined in the SOC; and familiarity with basic sensitivity protocols such as the use of preferred gender pronoun and name (Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

3. Continuing education in the assessment and development of communication skills in transsexual, transgender, and gender nonconforming clients. This may include attendance at professional meetings, workshops, or seminars; participation in research related to gender identity issues; independent study; or mentoring from an experienced, certified clinician.

Other professionals such as vocal coaches, theatre professionals, singing teachers, and movement experts may play a valuable adjunct role. Such professionals will ideally have experience working with, or be actively collaborating with, speech-language pathologists.

Assessment and Treatment Considerations

The overall purpose of voice and communication therapy is to help clients adapt their voice and communication in a way that is both safe and authentic, resulting in communication patterns that clients feel are congruent with their gender identity and that reflect their sense of self (Adler, Hirsch, & Mordaunt, 2006). It is essential that voice and communication specialists be sensitive to individual communication preferences. Communication – style, voice, choice of language, etc. – is personal. Individuals should not be counseled to adopt behaviors with which they are not comfortable or which do not feel authentic. Specialists can best serve their clients by taking the time to understand a person's gender concerns and goals for gender role expression (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia).

Individuals may choose the communication behaviors that they wish to acquire in accordance with their gender identity. These decisions are also informed and supported by the knowledge of the voice and communication specialist and by the assessment data for a specific client (Hancock, Krissinger, & Owen, 2010). Assessment includes a client's self-evaluation and a specialist's evaluation of voice, resonance, articulation, spoken language, and non-verbal communication (Adler et al., 2006; Hancock et al., 2010).

Voice and communication treatment plans are developed by considering the available research evidence, the clinical knowledge and experience of the specialist, and the client's own goals and values (American Speech-Language-Hearing Association, 2011; Canadian Association of Speech-Language Pathologists and Audiologists; Royal College of Speech Therapists, United Kingdom; Speech Pathology Australia; Vancouver Coastal Health, Vancouver, British Columbia, Canada). Targets of treatment typically include pitch, intonation, loudness and stress patterns, voice quality, resonance, articulation, speech rate and phrasing, language, and non-verbal communication (Adler et al., 2006; Davies & Goldberg, 2006; de Bruin, Coerts, & Greven, 2000; Gelfer, 1999; McNeill, 2006; Oates & Dacakis, 1983). Treatment may involve individual and/or group sessions. The frequency and duration of treatment will vary according to a client's needs. Existing protocols for voice and

communication treatment can be considered in developing an individualized therapy plan (Carew, Dacakis, & Oates, 2007; Dacakis, 2000; Davies & Goldberg, 2006; Gelfer, 1999; McNeill, Wilson, Clark, & Deakin, 2008; Mount & Salmon, 1988).

Feminizing or masculinizing the voice involves non-habitual use of the voice production mechanism. Prevention measures are necessary to avoid the possibility of vocal misuse and long-term vocal damage. All voice and communication therapy services should therefore include a vocal health component (Adler et al., 2006).

Vocal Health Considerations after Voice Feminization Surgery

As noted in section XI, some transsexual, transgender, and gender nonconforming people will undergo voice feminization surgery. (Voice deepening can be achieved through masculinizing hormone therapy, but feminizing hormones do not have an impact on the adult MtF voice.) There are varying degrees of satisfaction, safety, and long-term improvement in patients who have had such surgery. It is recommended that individuals undergoing voice feminization surgery also consult a voice and communication specialist to maximize the surgical outcome, help protect vocal health, and learn non-pitch related aspects of communication. Voice surgery procedures should include follow-up sessions with a voice and communication specialist who is licensed and/or credentialed by the board responsible for speech therapists/speech-language pathologists in that country (Kanagalingam et al., 2005; Neumann & Welzel, 2004).

XI

Surgery_

Sex Reassignment Surgery Is Effective and Medically Necessary

Surgery – particularly genital surgery – is often the last and the most considered step in the treatment process for gender dysphoria. While many transsexual, transgender, and gender nonconforming individuals find comfort with their gender identity, role, and expression without surgery, for many others surgery is essential and medically necessary to alleviate their gender dysphoria (Hage

& Karim, 2000). For the latter group, relief from gender dysphoria cannot be achieved without modification of their primary and/or secondary sex characteristics to establish greater congruence with their gender identity. Moreover, surgery can help patients feel more at ease in the presence of sex partners or in venues such as physicians' offices, swimming pools, or health clubs. In some settings, surgery might reduce risk of harm in the event of arrest or search by police or other authorities.

Follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well being, cosmesis, and sexual function (De Cuypere et al., 2005; Gijs & Brewaeys, 2007; Klein & Gorzalka, 2009; Pfäfflin & Junge, 1998). Additional information on the outcomes of surgical treatments are summarized in Appendix D.

Ethical Questions Regarding Sex Reassignment Surgery

In ordinary surgical practice, pathological tissues are removed to restore disturbed functions, or alterations are made to body features to improve a patient's self image. Some people, including some health professionals, object on ethical grounds to surgery as a treatment for gender dysphoria, because these conditions are thought not to apply.

It is important that health professionals caring for patients with gender dysphoria feel comfortable about altering anatomically normal structures. In order to understand how surgery can alleviate the psychological discomfort and distress of individuals with gender dysphoria, professionals need to listen to these patients discuss their symptoms, dilemmas, and life histories. The resistance against performing surgery on the ethical basis of "above all do no harm" should be respected, discussed, and met with the opportunity to learn from patients themselves about the psychological distress of having gender dysphoria and the potential for harm caused by denying access to appropriate treatments.

Genital and breast/chest surgical treatments for gender dysphoria are not merely another set of elective procedures. Typical elective procedures involve only a private mutually consenting contract between a patient and a surgeon. Genital and breast/chest surgeries as medically necessary treatments for gender dysphoria are to be undertaken only after assessment of the patient by qualified mental health professionals, as outlined in section VII of the SOC. These surgeries may be performed once there is written documentation that this assessment has occurred and that the person has met the criteria for a specific surgical treatment. By following this procedure, mental health professionals, surgeons, and of course patients, share responsibility for the decision to make irreversible changes to the body.

It is unethical to deny availability or eligibility for sex reassignment surgeries solely on the basis of blood seropositivity for blood-borne infections such as HIV or hepatitis C or B.

Relationship of Surgeons with Mental Health Professionals, Hormone-Prescribing Physicians (if Applicable), and Patients (Informed Consent)

The role of a surgeon in the treatment of gender dysphoria is not that of a mere technician. Rather, conscientious surgeons will have insight into each patient's history and the rationale that led to the referral for surgery. To that end, surgeons must talk at length with their patients and have close working relationships with other health professionals who have been actively involved in their clinical care.

Consultation is readily accomplished when a surgeon practices as part of an interdisciplinary health care team. In the absence of this, a surgeon must be confident that the referring mental health professional(s), and if applicable the physician who prescribes hormones, are competent in the assessment and treatment of gender dysphoria, because the surgeon is relying heavily on their expertise.

Once a surgeon is satisfied that the criteria for specific surgeries have been met (as outlined below), surgical treatment should be considered and a preoperative surgical consultation should take place. During this consultation, the procedure and postoperative course should be extensively discussed with the patient. Surgeons are responsible for discussing all of the following with patients seeking surgical treatments for gender dysphoria:

- The different surgical techniques available (with referral to colleagues who provide alternative options);
- The advantages and disadvantages of each technique;
- The limitations of a procedure to achieve “ideal” results; surgeons should provide a full range of before-and-after photographs of their own patients, including both successful and unsuccessful outcomes;
- The inherent risks and possible complications of the various techniques; surgeons should inform patients of their own complication rates with each procedure.

These discussions are the core of the informed consent process, which is both an ethical and legal requirement for any surgical procedure. Ensuring that patients have a realistic expectation of outcomes is important in achieving a result that will alleviate their gender dysphoria.

All of this information should be provided to patients in writing, in a language in which they are fluent, and in graphic illustrations. Patients should receive the information in advance (possibly via the internet) and given ample time to review it carefully. The elements of informed consent should always be discussed face-to-face prior to the surgical intervention. Questions can then be answered and written informed consent can be provided by the patient. Because these surgeries are irreversible, care should be taken to ensure that patients have sufficient time to absorb information fully before they are asked to provide informed consent. A minimum of 24 hours is suggested.

Surgeons should provide immediate aftercare and consultation with other physicians serving the patient in the future. Patients should work with their surgeon to develop an adequate aftercare plan for the surgery.

Overview of Surgical Procedures for the Treatment of Patients with Gender Dysphoria

For the male-to-female (MtF) patient, surgical procedures may include the following:

1. Breast/chest surgery: augmentation mammoplasty (implants/lipofilling);
2. Genital surgery: penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty;
3. Non-genital, non-breast surgical interventions: facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction, and various aesthetic procedures.

For the female-to-male (FtM) patient, surgical procedures may include the following:

1. Breast/chest surgery: subcutaneous mastectomy, creation of a male chest;
2. Genital surgery: hysterectomy/ovariectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty (employing a pedicled or free vascularized flap), vaginectomy, scrotoplasty, and implantation of erection and/or testicular prostheses;

3. Non-genital, non-breast surgical interventions: voice surgery (rare), liposuction, lipofilling, pectoral implants, and various aesthetic procedures.

Reconstructive Versus Aesthetic Surgery

The question of whether sex reassignment surgery should be considered “aesthetic” surgery or “reconstructive” surgery is pertinent not only from a philosophical point of view, but also from a financial point of view. Aesthetic or cosmetic surgery is mostly regarded as not medically necessary and therefore is typically paid for entirely by the patient. In contrast, reconstructive procedures are considered medically necessary – with unquestionable therapeutic results – and thus paid for partially or entirely by national health systems or insurance companies.

Unfortunately, in the field of plastic and reconstructive surgery (both in general and specifically for gender-related surgeries), there is no clear distinction between what is purely reconstructive and what is purely cosmetic. Most plastic surgery procedures actually are a mixture of both reconstructive and cosmetic components.

While most professionals agree that genital surgery and mastectomy cannot be considered purely cosmetic, opinions diverge as to what degree other surgical procedures (e.g., breast augmentation, facial feminization surgery) can be considered purely reconstructive. Although it may be much easier to see a phalloplasty or a vaginoplasty as an intervention to end lifelong suffering, for certain patients an intervention like a reduction rhinoplasty can have a radical and permanent effect on their quality of life, and therefore is much more medically necessary than for somebody without gender dysphoria.

Criteria for Surgeries

As for all of the SOC, the criteria for initiation of surgical treatments for gender dysphoria were developed to promote optimal patient care. While the SOC allow for an individualized approach to best meet a patient’s health care needs, a criterion for all breast/chest and genital surgeries is documentation of persistent gender dysphoria by a qualified mental health professional. For some surgeries, additional criteria include preparation and treatment consisting of feminizing/masculinizing hormone therapy and one year of continuous living in a gender role that is congruent with one’s gender identity.

These criteria are outlined below. Based on the available evidence and expert clinical consensus, different recommendations are made for different surgeries.

The SOC do not specify an order in which different surgeries should occur. The number and sequence of surgical procedures may vary from patient to patient, according to their clinical needs.

Criteria for breast/chest surgery (one referral)

Criteria for mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a pre-requisite.

Criteria for breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for genital surgery (two referrals)

The criteria for genital surgery are specific to the type of surgery being requested.

Criteria for hysterectomy and ovariectomy in FtM patients and for orchiectomy in MtF patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled.
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before the patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these procedures for medical indications other than gender dysphoria.

Criteria for metoidioplasty or phalloplasty in FtM patients and for vaginoplasty in MtF patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).
6. 12 continuous months of living in a gender role that is congruent with their gender identity;

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

Rationale for a preoperative, 12-month experience of living in an identity-congruent gender role:

The criterion noted above for some types of genital surgeries – i.e., that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity – is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery. As noted in section VII, the social aspects of changing one's gender role are usually challenging – often more so than the physical aspects. Changing gender role can have profound personal and social consequences, and the decision to do so should include an awareness of what the familial, interpersonal, educational, vocational, economic, and legal challenges are likely to be, so that people can function successfully in their gender role. Support from a qualified mental health professional and from peers can be invaluable in ensuring a successful gender role adaptation (Bockting, 2008).

The duration of 12 months allows for a range of different life experiences and events that may occur throughout the year (e.g., family events, holidays, vacations, season-specific work or school experiences). During this time, patients should present consistently, on a day-to-day basis and across all settings of life, in their desired gender role. This includes coming out to partners, family, friends, and community members (e.g., at school, work, other settings).

Health professionals should clearly document a patient's experience in the gender role in the medical chart, including the start date of living full time for those who are preparing for genital surgery. In some situations, if needed, health professionals may request verification that this criterion has been fulfilled: They may communicate with individuals who have related to the patient in an identity-congruent gender role, or request documentation of a legal name and/or gender marker change, if applicable.

Surgery for Persons with Psychotic Conditions and Other Serious Mental Illnesses

When patients with gender dysphoria are also diagnosed with severe psychiatric disorders and impaired reality testing (e.g., psychotic episodes, bipolar disorder, dissociative identity disorder, borderline personality disorder), an effort must be made to improve these conditions with psychotropic medications and/or psychotherapy before surgery is contemplated. Reevaluation by a mental health professional qualified to assess and manage psychotic conditions should be

conducted prior to surgery, describing the patient's mental status and readiness for surgery. It is preferable that this mental health professional be familiar with the patient. No surgery should be performed while a patient is actively psychotic (De Cuypere & Vercruysse, 2009).

Competency of Surgeons Performing Breast/Chest or Genital Surgery

Physicians who perform surgical treatments for gender dysphoria should be urologists, gynecologists, plastic surgeons, or general surgeons, and board-certified as such by the relevant national and/or regional association. Surgeons should have specialized competence in genital reconstructive techniques as indicated by documented supervised training with a more experienced surgeon. Even experienced surgeons must be willing to have their surgical skills reviewed by their peers. An official audit of surgical outcomes and publication of these results would be greatly reassuring to both referring health professionals and patients. Surgeons should regularly attend professional meetings where new techniques are presented. The internet is often effectively used by patients to share information on their experience with surgeons and their teams.

Ideally, surgeons should be knowledgeable about more than one surgical technique for genital reconstruction so that they, in consultation with patients, can choose the ideal technique for each individual. Alternatively, if a surgeon is skilled in a single technique and this procedure is either not suitable for or desired by a patient, the surgeon should inform the patient about other procedures and offer referral to another appropriately skilled surgeon.

Breast/Chest Surgery Techniques and Complications

Although breast/chest appearance is an important secondary sex characteristic, breast presence or size is not involved in the legal definitions of sex and gender and is not necessary for reproduction. The performance of breast/chest operations for treatment of gender dysphoria should be considered with the same care as beginning hormone therapy, as both produce relatively irreversible changes to the body.

For the MtF patient, a breast augmentation (sometimes called “chest reconstruction”) is not different from the procedure in a natal female patient. It is usually performed through implantation of breast prostheses and occasionally with the lipofilling technique. Infections and capsular fibrosis are rare complications of augmentation mammoplasty in MtF patients (Kanhai, Hage, Karim, & Mulder, 1999).

For the FtM patient, a mastectomy or “male chest contouring” procedure is available. For many FtM patients, this is the only surgery undertaken. When the amount of breast tissue removed requires skin removal, a scar will result and the patient should be so informed. Complications of subcutaneous mastectomy can include nipple necrosis, contour irregularities, and unsightly scarring (Monstrey et al., 2008).

Genital Surgery Techniques and Complications

Genital surgical procedures for the MtF patient may include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. Techniques include penile skin inversion, pedicled colosigmoid transplant, and free skin grafts to line the neovagina. Sexual sensation is an important objective in vaginoplasty, along with creation of a functional vagina and acceptable cosmesis.

Surgical complications of MtF genital surgery may include complete or partial necrosis of the vagina and labia, fistulas from the bladder or bowel into the vagina, stenosis of the urethra, and vaginas that are either too short or too small for coitus. While the surgical techniques for creating a neovagina are functionally and aesthetically excellent, anorgasmia following the procedure has been reported, and a second stage labiaplasty may be needed for cosmesis (Klein & Gorzalka, 2009; Lawrence, 2006).

Genital surgical procedures for FtM patients may include hysterectomy, ovariectomy (salpingo-oophorectomy), vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty. For patients without former abdominal surgery, the laparoscopic technique for hysterectomy and salpingo-oophorectomy is recommended to avoid a lower-abdominal scar. Vaginal access may be difficult as most patients are nulliparous and have often not experienced penetrative intercourse. Current operative techniques for phalloplasty are varied. The choice of techniques may be restricted by anatomical or surgical considerations and by a client's financial considerations. If the objectives of phalloplasty are a neophallus of good appearance, standing micturition, sexual sensation, and/or coital ability, patients should be clearly informed that there are several separate stages of surgery and frequent technical difficulties, which may require additional operations. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one operation. The objective of standing micturition with this technique can not always be ensured (Monstrey et al., 2009).

Complications of phalloplasty in FtMs may include frequent urinary tract stenoses and fistulas, and occasionally necrosis of the neophallus. Metoidioplasty results in a micropenis, without the capacity for standing urination. Phalloplasty, using a pedicled or a free vascularized flap, is a lengthy, multi-stage procedure with significant morbidity that includes frequent urinary complications and

unavoidable donor site scarring. For this reason, many FtM patients never undergo genital surgery other than hysterectomy and salpingo-oophorectomy (Hage & De Graaf, 1993).

Even patients who develop severe surgical complications seldom regret having undergone surgery. The importance of surgery can be appreciated by the repeated finding that quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2006).

Other Surgeries

Other surgeries for assisting in body feminization include reduction thyroid chondroplasty (reduction of the Adam's apple), voice modification surgery, suction-assisted lipoplasty (contour modeling) of the waist, rhinoplasty (nose correction), facial bone reduction, face-lift, and blepharoplasty (rejuvenation of the eyelid). Other surgeries for assisting in body masculinization include liposuction, lipofilling, and pectoral implants. Voice surgery to obtain a deeper voice is rare but may be recommended in some cases, such as when hormone therapy has been ineffective.

Although these surgeries do not require referral by mental health professionals, such professionals can play an important role in assisting clients in making a fully informed decision about the timing and implications of such procedures in the context of the social transition.

Although most of these procedures are generally labeled “purely aesthetic,” these same operations in an individual with severe gender dysphoria can be considered medically necessary, depending on the unique clinical situation of a given patient's condition and life situation. This ambiguity reflects reality in clinical situations, and allows for individual decisions as to the need and desirability of these procedures.

XII

Postoperative Care and Follow-up

Long-term postoperative care and follow-up after surgical treatments for gender dysphoria are associated with good surgical and psychosocial outcomes (Monstrey et al., 2009). Follow-up is important to a patient's subsequent physical and mental health and to a surgeon's knowledge about the benefits and limitations of surgery. Surgeons who operate on patients coming from long

distances should include personal follow-up in their care plan and attempt to ensure affordable local long-term aftercare in their patients' geographic region.

Postoperative patients may sometimes exclude themselves from follow-up by specialty providers, including the hormone-prescribing physician (for patients receiving hormones), not recognizing that these providers are often best able to prevent, diagnose, and treat medical conditions that are unique to hormonally and surgically treated patients. The need for follow-up equally extends to mental health professionals, who may have spent a longer period of time with the patient than any other professional and therefore are in an excellent position to assist in any postoperative adjustment difficulties. Health professionals should stress the importance of postoperative follow-up care with their patients and offer continuity of care.

Postoperative patients should undergo regular medical screening according to recommended guidelines for their age. This is discussed more in the next section.

XIII

Lifelong Preventive and Primary Care

Transsexual, transgender, and gender nonconforming people need health care throughout their lives. For example, to avoid the negative secondary effects of having a gonadectomy at a relatively young age and/or receiving long-term, high-dose hormone therapy, patients need thorough medical care by providers experienced in primary care and transgender health. If one provider is not able to provide all services, ongoing communication among providers is essential.

Primary care and health maintenance issues should be addressed before, during, and after any possible changes in gender role and medical interventions to alleviate gender dysphoria. While hormone providers and surgeons play important roles in preventive care, every transsexual, transgender, and gender nonconforming person should partner with a primary care provider for overall health care needs (Feldman, 2007).

General Preventive Health Care

Screening guidelines developed for the general population are appropriate for organ systems that are unlikely to be affected by feminizing/masculinizing hormone therapy. However, in areas such

as cardiovascular risk factors, osteoporosis, and some cancers (breast, cervical, ovarian, uterine, and prostate), such general guidelines may either over- or underestimate the cost-effectiveness of screening individuals who are receiving hormone therapy.

Several resources provide detailed protocols for the primary care of patients undergoing feminizing/masculinizing hormone therapy, including therapy that is provided after sex reassignment surgeries (Center of Excellence for Transgender Health, UCSF, 2011; Feldman & Goldberg, 2006; Feldman, 2007; Gorton, Buth, & Spade, 2005). Clinicians should consult their national evidence-based guidelines and discuss screening with their patients in light of the effects of hormone therapy on their baseline risk.

Cancer Screening

Cancer screening of organ systems that are associated with sex can present particular medical and psychosocial challenges for transsexual, transgender, and gender nonconforming patients and their health care providers. In the absence of large-scale prospective studies, providers are unlikely to have enough evidence to determine the appropriate type and frequency of cancer screenings for this population. Over-screening results in higher health care costs, high false positive rates, and often unnecessary exposure to radiation and/or diagnostic interventions such as biopsies. Under-screening results in diagnostic delay for potentially treatable cancers. Patients may find cancer screening gender affirming (such as mammograms for MtF patients) or both physically and emotionally painful (such as Pap smears offer continuity of care for FtM patients).

Urogenital Care

Gynecologic care may be necessary for transsexual, transgender, and gender nonconforming people of both sexes. For FtM patients, such care is needed predominantly for individuals who have not had genital surgery. For MtF patients, such care is needed after genital surgery. While many surgeons counsel patients regarding postoperative urogenital care, primary care clinicians and gynecologists should also be familiar with the special genital concerns of this population.

All MtF patients should receive counseling regarding genital hygiene, sexuality, and prevention of sexually transmitted infections; those who have had genital surgery should also be counseled on the need for regular vaginal dilation or penetrative intercourse in order to maintain vaginal depth and width (van Trotsenburg, 2009). Due to the anatomy of the male pelvis, the axis and the dimensions

of the neovagina differ substantially from those of a biologic vagina. This anatomic difference can affect intercourse if not understood by MtF patients and their partners (van Trotsenburg, 2009).

Lower urinary tract infections occur frequently in MtF patients who have had surgery because of the reconstructive requirements of the shortened urethra. In addition, these patients may suffer from functional disorders of the lower urinary tract; such disorders may be caused by damage of the autonomous nerve supply of the bladder floor during dissection between the rectum and the bladder, and by a change of the position of the bladder itself. A dysfunctional bladder (e.g., overactive bladder, stress or urge urinary incontinence) may occur after sex reassignment surgery (Hoebeke et al., 2005; Kuhn, Hildebrand, & Birkhauser, 2007).

Most FtM patients do not undergo vaginectomy (colpectomy). For patients who take masculinizing hormones, despite considerable conversion of testosterone to estrogens, atrophic changes of the vaginal lining can be observed regularly and may lead to pruritus or burning. Examination can be both physically and emotionally painful, but lack of treatment can seriously aggravate the situation. Gynecologists treating the genital complaints of FtM patients should be aware of the sensitivity that patients with a male gender identity and masculine gender expression might have around having genitals typically associated with the female sex.

XIV

Applicability of the Standards of Care to People Living in Institutional Environments

The SOC in their entirety apply to all transsexual, transgender, and gender nonconforming people, irrespective of their housing situation. People should not be discriminated against in their access to appropriate health care based on where they live, including institutional environments such as prisons or long-/intermediate-term health care facilities (Brown, 2009). Health care for transsexual, transgender, and gender nonconforming people living in an institutional environment should mirror that which would be available to them if they were living in a non-institutional setting within the same community.

All elements of assessment and treatment as described in the SOC can be provided to people living in institutions (Brown, 2009). Access to these medically necessary treatments should not be denied on the basis of institutionalization or housing arrangements. If the in-house expertise of health professionals in the direct or indirect employ of the institution does not exist to assess

and/or treat people with gender dysphoria, it is appropriate to obtain outside consultation from professionals who are knowledgeable about this specialized area of health care.

People with gender dysphoria in institutions may also have co-existing mental health conditions (Cole et al., 1997). These conditions should be evaluated and treated appropriately.

People who enter an institution on an appropriate regimen of hormone therapy should be continued on the same, or similar, therapies and monitored according to the SOC. A “freeze frame” approach is not considered appropriate care in most situations (Kosilek v. Massachusetts Department of Corrections/Maloney, C.A. No. 92-12820-MLW, 2002). People with gender dysphoria who are deemed appropriate for hormone therapy (following the SOC) should be started on such therapy. The consequences of abrupt withdrawal of hormones or lack of initiation of hormone therapy when medically necessary include a high likelihood of negative outcomes such as surgical self-treatment by autocastration, depressed mood, dysphoria, and/or suicidality (Brown, 2010).

Reasonable accommodations to the institutional environment can be made in the delivery of care consistent with the SOC, if such accommodations do not jeopardize the delivery of medically necessary care to people with gender dysphoria. An example of a reasonable accommodation is the use of injectable hormones, if not medically contraindicated, in an environment where diversion of oral preparations is highly likely (Brown, 2009). Denial of needed changes in gender role or access to treatments, including sex reassignment surgery, on the basis of residence in an institution are not reasonable accommodations under the SOC (Brown, 2010).

Housing and shower/bathroom facilities for transsexual, transgender, and gender nonconforming people living in institutions should take into account their gender identity and role, physical status, dignity, and personal safety. Placement in a single-sex housing unit, ward, or pod on the sole basis of the appearance of the external genitalia may not be appropriate and may place the individual at risk for victimization (Brown, 2009).

Institutions where transsexual, transgender, and gender nonconforming people reside and receive health care should monitor for a tolerant and positive climate to ensure that residents are not under attack by staff or other residents.

XV

Applicability of the Standards of Care to People With Disorders of Sex Development

Terminology

The term *disorder of sex development* (DSD) refers to a somatic condition of atypical development of the reproductive tract (Hughes, Houk, Ahmed, Lee, & LWPE1/ESPE2 Consensus Group, 2006). DSDs include the condition that used to be called *intersexuality*. Although the terminology was changed to *DSD* during an international consensus conference in 2005 (Hughes et al., 2006), disagreement about language use remains. Some people object strongly to the “disorder” label, preferring instead to view these congenital conditions as a matter of diversity (Diamond, 2009) and to continue using the terms *intersex* or *intersexuality*. In the SOC, WPATH uses the term *DSD* in an objective and value-free manner, with the goal of ensuring that health professionals recognize this medical term and use it to access relevant literature as the field progresses. WPATH remains open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Rationale for Addition to the SOC

Previously, individuals with a DSD who also met the *DSM-IV-TR*’s behavioral criteria for Gender Identity Disorder (American Psychiatric Association, 2000) were excluded from that general diagnosis. Instead, they were categorized as having a “Gender Identity Disorder - Not Otherwise Specified.” They were also excluded from the WPATH *Standards of Care*.

The current proposal for *DSM-5* (www.dsm5.org) is to replace the term *gender identity disorder* with *gender dysphoria*. Moreover, the proposed changes to the *DSM* consider gender dysphoric people with a DSD to have a subtype of gender dysphoria. This proposed categorization – which explicitly differentiates between gender dysphoric individuals with and without a DSD – is justified: In people with a DSD, gender dysphoria differs in its phenomenological presentation, epidemiology, life trajectories, and etiology (Meyer-Bahlburg, 2009).

Adults with a DSD and gender dysphoria have increasingly come to the attention of health professionals. Accordingly, a brief discussion of their care is included in this version of the SOC.

Health History Considerations

Health professionals assisting patients with both a DSD and gender dysphoria need to be aware that the medical context in which such patients have grown up is typically very different from that of people without a DSD.

Some people are recognized as having a DSD through the observation of gender-atypical genitals at birth. (Increasingly this observation is made during the prenatal period by way of imaging procedures such as ultrasound.) These infants then undergo extensive medical diagnostic procedures. After consultation among the family and health professionals – during which the specific diagnosis, physical and hormonal findings, and feedback from long-term outcome studies (Cohen-Kettenis, 2005; Dessens, Slijper, & Drop, 2005; Jurgensen, Hiort, Holterhus, & Thyen, 2007; Mazur, 2005; Meyer-Bahlburg, 2005; Stikkelbroeck et al., 2003; Wisniewski, Migeon, Malouf, & Gearhart, 2004) are considered – the newborn is assigned a sex, either male or female.

Other individuals with a DSD come to the attention of health professionals around the age of puberty through the observation of atypical development of secondary sex characteristics. This observation also leads to a specific medical evaluation.

The type of DSD and severity of the condition has significant implications for decisions about a patient's initial sex assignment, subsequent genital surgery, and other medical and psychosocial care (Meyer-Bahlburg, 2009). For instance, the degree of prenatal androgen exposure in individuals with a DSD has been correlated with the degree of masculinization of gender-related *behavior* (that is, *gender role and expression*); however, the correlation is only moderate, and considerable behavioral variability remains unaccounted for by prenatal androgen exposure (Jurgensen et al., 2007; Meyer-Bahlburg, Dolezal, Baker, Ehrhardt, & New, 2006). Notably, a similar correlation of prenatal hormone exposure with gender *identity* has not been demonstrated (e.g., Meyer-Bahlburg et al., 2004). This is underlined by the fact that people with the same (core) gender identity can vary widely in the degree of masculinization of their gender-related behavior.

Assessment and Treatment of Gender Dysphoria in People with Disorders of Sex Development

Very rarely are individuals with a DSD identified as having gender dysphoria *before* a DSD diagnosis has been made. Even so, a DSD diagnosis is typically apparent with an appropriate history and basic physical exam – both of which are part of a medical evaluation for the appropriateness of hormone therapy or surgical interventions for gender dysphoria. Mental health professionals should ask their clients presenting with gender dysphoria to have a physical exam, particularly if they are not currently seeing a primary care (or other health care) provider.

Most people with a DSD who are born with genital ambiguity do not develop gender dysphoria (e.g., Meyer-Bahlburg et al., 2004; Wisniewski et al., 2004). However, some people with a DSD will develop chronic gender dysphoria and even undergo a change in their birth-assigned sex and/or their gender role (Meyer-Bahlburg, 2005; Wilson, 1999; Zucker, 1999). If there are persistent and strong indications that gender dysphoria is present, a comprehensive evaluation by clinicians skilled in the assessment and treatment of gender dysphoria is essential, irrespective of the patient's age. Detailed recommendations have been published for conducting such an assessment and for making treatment decisions to address gender dysphoria in the context of a DSD (Meyer-Bahlburg, in press). Only after thorough assessment should steps be taken in the direction of changing a patient's birth-assigned sex or gender role.

Clinicians assisting these patients with treatment options to alleviate gender dysphoria may profit from the insights gained from providing care to patients without a DSD (Cohen-Kettenis, 2010). However, certain criteria for treatment (e.g., age, duration of experience with living in the desired gender role) are usually not routinely applied to people with a DSD; rather, the criteria are interpreted in light of a patient's specific situation (Meyer-Bahlburg, in press). In the context of a DSD, changes in birth-assigned sex and gender role have been made at any age between early elementary-school age and middle adulthood. Even genital surgery may be performed much earlier in these patients than in gender dysphoric individuals without a DSD if the surgery is well justified by the diagnosis, by the evidence-based gender-identity prognosis for the given syndrome and syndrome severity, and by the patient's wishes.

One reason for these treatment differences is that genital surgery in individuals with a DSD is quite common in infancy and adolescence. Infertility may already be present due to either early gonadal failure or to gonadectomy because of a malignancy risk. Even so, it is advisable for patients with a DSD to undergo a full social transition to another gender role only if there is a long-standing history of gender-atypical behavior, and if gender dysphoria and/or the desire to change one's gender role has been strong and persistent for a considerable period of time. Six months is the time period of full symptom expression required for the application of the gender dysphoria diagnosis proposed for *DSM-5* (Meyer-Bahlburg, in press).

Additional Resources

The gender-relevant medical histories of people with a DSD are often complex. Their histories may include a great variety of inborn genetic, endocrine, and somatic atypicalities, as well as various hormonal, surgical, and other medical treatments. For this reason, many additional issues need to be considered in the psychosocial and medical care of such patients, regardless of the presence of gender dysphoria. Consideration of these issues is beyond what can be covered in the SOC. The interested reader is referred to existing publications (e.g., Cohen-Kettenis & Pfäfflin, 2003; Meyer-Bahlburg, 2002, 2008). Some families and patients also find it useful to consult or work with community support groups.

There is a very substantial medical literature on the medical management of patients with a DSD. Much of this literature has been produced by high-level specialists in pediatric endocrinology and urology, with input from specialized mental health professionals, especially in the area of gender. Recent international consensus conferences have addressed evidence-based care guidelines (including issues of gender and of genital surgery) for DSD in general (Hughes et al., 2006) and specifically for Congenital Adrenal Hyperplasia (Joint LWPES/ESPE CAH Working Group et al., 2002; Speiser et al., 2010). Others have addressed the research needs for DSD in general (Meyer-Bahlburg & Blizzard, 2004) and for selected syndromes such as 46,XXY (Simpson et al., 2003).



References

Abramowitz, S. I. (1986). Psychosocial outcomes of sex reassignment surgery. <i>Journal of Consulting and Clinical Psychology</i> , 54(2), 183-189. doi:10.1037/0022-006X.54.2.183	Adler, R. K., Hirsch, S., & Mordaunt, M. (2006). <i>Voice and communication therapy for the transgender/transsexual client: A comprehensive clinical guide</i> . San Diego, CA: Plural Pub.
ACOG Committee of Gynecologic Practice. (2005). Committee opinion #322: Compounded bioidentical hormones. <i>Obstetrics & Gynecology</i> , 106(5), 139-140.	American Academy of Family Physicians. (2005). <i>Definition of family medicine</i> . Retrieved August 10, 2009, from http://www.aafp.org/online/en/home/policy/policies/f/fammeddef.html

- American Medical Association. (2008). *Resolution 122 (A-08)*. Retrieved from <http://www.ama-assn.org/ama1/pub/upload/mm/471/122.doc>
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4th ed., text rev.). Washington, DC: Author.
- American Speech-Language-Hearing Association. (2011). *Scope of practice*. Retrieved from www.asha.org
- Anton, B. S. (2009). Proceedings of the American Psychological Association for the legislative year 2008: Minutes of the annual meeting of the council of representatives, February 22-24, 2008, Washington, DC, and August 13 and 17, 2008, Boston, MA, and minutes of the February, June, August, and December 2008 meetings of the board of directors. *American Psychologist*, 64, 372-453. doi:10.1037/a0015932
- Asscheman, H., Giltay, E. J., Megens, J. A. J., de Ronde, W., van Trotsenburg, M. A. A., & Gooren, L. J. G. (2011). A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *European Journal of Endocrinology*, 164(4), 635-642. doi:10.1530/EJE-10-1038
- Baba, T., Endo, T., Honnma, H., Kitajima, Y., Hayashi, T., Ikeda, H., . . . Saito, T. (2007). Association between polycystic ovary syndrome and female-to-male transsexuality. *Human Reproduction*, 22(4), 1011-1016. doi:10.1093/humrep/del474
- Bakker, A., Van Kesteren, P. J., Gooren, L. J., & Bezemer, P. D. (1993). The prevalence of transsexualism in the Netherlands. *Acta Psychiatrica Scandinavica*, 87(4), 237-238. doi:10.1111/j.1600-0447.1993.tb03364.x
- Balen, A. H., Schachter, M. E., Montgomery, D., Reid, R. W., & Jacobs, H. S. (1993). Polycystic ovaries are a common finding in untreated female to male transsexuals. *Clinical Endocrinology*, 38(3), 325-329. doi:10.1111/j.1365-2265.1993.tb01013.x
- Basson, R. (2001). Towards optimal hormonal treatment of male to female gender identity disorder. *Journal of Sexual and Reproductive Medicine*, 1(1), 45-51.
- Basson, R., & Prior, J. C. (1998). Hormonal therapy of gender dysphoria: The male-to-female transsexual. In D. Denny (Ed.), *Current concepts in transgender identity* (pp. 277-296). New York: Garland Publishing, Inc.
- Benjamin, H. (1966). *The transsexual phenomenon*. New York: Julian Press.
- Besnier, N. (1994). Polynesian gender liminality through time and space. In G. Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history* (pp. 285-328). New York: Zone Books.
- Bockting, W. O. (1999). From construction to context: Gender through the eyes of the transgendered. *Siecus Report*, 28(1), 3-7.

- Bockting, W. O. (2008). Psychotherapy and the real-life experience: From gender dichotomy to gender diversity. *Sexologies*, 17(4), 211-224. doi:10.1016/j.sexol.2008.08.001
- Bockting, W. O., & Coleman, E. (2007). Developmental stages of the transgender coming out process: Toward an integrated identity. In R. Ettner, S. Monstrey & A. Eyler (Eds.), *Principles of transgender medicine and surgery* (pp. 185-208). New York: The Haworth Press.
- Bockting, W. O., & Goldberg, J. M. (2006). Guidelines for transgender care (special issue). *International Journal of Transgenderism*, 9(3/4).
- Bockting, W. O., Knudson, G., & Goldberg, J. M. (2006). Counseling and mental health care for transgender adults and loved ones. *International Journal of Transgenderism*, 9(3/4), 35-82. doi:10.1300/J485v09n03_03
- Bolin, A. (1988). *In search of Eve* (pp. 189-192). New York: Bergin & Garvey.
- Bolin, A. (1994). Transcending and transgendering: Male-to-female transsexuals, dichotomy and diversity. In G. Herdt (Ed.), *Third sex, third gender: Beyond sexual dimorphism in culture and history* (pp. 447-486). New York: Zone Books.
- Bornstein, K. (1994). *Gender outlaw: On men, women, and the rest of us*. New York: Routledge.
- Bosinski, H. A. G., Peter, M., Bonatz, G., Arndt, R., Heidenreich, M., Sippell, W. G., & Wille, R. (1997). A higher rate of hyperandrogenic disorders in female-to-male transsexuals. *Psychoneuroendocrinology*, 22(5), 361-380. doi:10.1016/S0306-4530(97)00033-4
- Brill, S. A., & Pepper, R. (2008). *The transgender child: A handbook for families and professionals*. Berkeley, CA: Cleis Press.
- Brown, G. R. (2009). Recommended revisions to The World Professional Association for Transgender Health's Standards of Care section on medical care for incarcerated persons with gender identity disorder. *International Journal of Transgenderism*, 11(2), 133-139. doi:10.1080/15532730903008073
- Brown, G. R. (2010). Autocastration and autopenectomy as surgical self-treatment in incarcerated persons with gender identity disorder. *International Journal of Transgenderism*, 12(1), 31-39. doi:10.1080/15532731003688970
- Bullough, V. L., & Bullough, B. (1993). *Cross dressing, sex, and gender*. Philadelphia, PA: University of Pennsylvania Press.
- Callen Lorde Community Health Center. (2000). *Transgender health program protocols*. Retrieved from http://www.callen-lorde.org/documents/TG_Protocol_Request_Form2.pdf

- Callen Lorde Community Health Center. (2011). *Transgender health program protocols*. Retrieved from http://www.callen-lorde.org/documents/TG_Protocol_Request_Form2.pdf
- Canadian Association of Speech-Language Pathologists and Audiologists. <http://www.caspa.ca/>
- Carew, L., Dacakis, G., & Oates, J. (2007). The effectiveness of oral resonance therapy on the perception of femininity of voice in male-to-female transsexuals. *Journal of Voice*, 21(5), 591-603. doi:10.1016/j.jvoice.2006.05.005
- Carnegie, C. (2004). Diagnosis of hypogonadism: Clinical assessments and laboratory tests. *Reviews in Urology*, 6(Suppl 6), S3-8.
- Cattrall, F. R., & Healy, D. L. (2004). Long-term metabolic, cardiovascular and neoplastic risks with polycystic ovary syndrome. *Best Practice & Research Clinical Obstetrics & Gynaecology*, 18(5), 803-812. doi:10.1016/j.bpobgyn.2004.05.005
- Center of Excellence for Transgender Health, UCSF. (2011). *Primary care protocol for transgender health care*. Retrieved from <http://transhealth.ucsf.edu/trans?page=protocol-00-00>
- Chiñas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque, NM: University of New Mexico Press.
- Clements, K., Wilkinson, W., Kitano, K., & Marx, R. (1999). HIV prevention and health service needs of the transgender community in San Francisco. *International Journal of Transgenderism*, 3(1), 2-17.
- Cohen-Kettenis, P. T. (2001). Gender identity disorder in DSM? *Journal of the American Academy of Child & Adolescent Psychiatry*, 40(4), 391-391. doi:10.1097/00004583-200104000-00006
- Cohen-Kettenis, P. T. (2005). Gender change in 46,XY persons with 5 α -reductase-2 deficiency and 17 α -hydroxysteroid dehydrogenase-3 deficiency. *Archives of Sexual Behavior*, 34(4), 399-410. doi:10.1007/s10508-005-4339-4
- Cohen-Kettenis, P. T. (2006). Gender identity disorders. In C. Gillberg, R. Harrington & H. C. Steinhausen (Eds.), *A clinician's handbook of child and adolescent psychiatry* (pp. 695-725). New York: Cambridge University Press.
- Cohen-Kettenis, P. T. (2010). Psychosocial and psychosexual aspects of disorders of sex development. *Best Practice & Research Clinical Endocrinology & Metabolism*, 24(2), 325-334. doi:10.1016/j.beem.2009.11.005
- Cohen-Kettenis, P. T., & Kuiper, A. J. (1984). Transseksualiteit en psychotherapie. *Tijdschrift Voor Psychotherapie*, 10, 153-166.

- Cohen-Kettenis, P. T., Owen, A., Kaijser, V. G., Bradley, S. J., & Zucker, K. J. (2003). Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. *Journal of Abnormal Child Psychology*, 31(1), 41-53. doi:10.1023/A:1021769215342
- Cohen-Kettenis, P. T., & Pfäfflin, F. (2003). *Transgenderism and intersexuality in childhood and adolescence: Making choices*. Thousand Oaks, CA: Sage Publications, Inc.
- Cohen-Kettenis, P. T., & Pfäfflin, F. (2010). The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Archives of Sexual Behavior*, 39(2), 499-513. doi:10.1007/s10508-009-9562-y
- Cohen-Kettenis, P. T., Schagen, S. E. E., Steensma, T. D., de Vries, A. L. C., & Delemarre-van de Waal, H. A. (2011). Puberty suppression in a gender-dysphoric adolescent: A 22-year follow-up. *Archives of Sexual Behavior*, 40(4), 843-847. doi:10.1007/s10508-011-9758-9
- Cohen-Kettenis, P. T., Wallien, M., Johnson, L. L., Owen-Anderson, A. F. H., Bradley, S. J., & Zucker, K. J. (2006). A parent-report gender identity questionnaire for children: A cross-national, cross-clinic comparative analysis. *Clinical Child Psychology and Psychiatry*, 11(3), 397-405. doi:10.1177/1359104506059135
- Cole, C. M., O'Boyle, M., Emory, L. E., & Meyer III, W. J. (1997). Comorbidity of gender dysphoria and other major psychiatric diagnoses. *Archives of Sexual Behavior*, 26(1), 13-26.
- Coleman, E., Colgan, P., & Gooren, L. (1992). Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Archives of Sexual Behavior*, 21(3), 313-321.
- Costa, L. M., & Matzner, A. (2007). *Male bodies, women's souls: Personal narratives of Thailand's transgendered youth*. Binghamton, NY: Haworth Press.
- Currah, P., Juang, R. M., & Minter, S. (2006). *Transgender rights*. Minneapolis, MN: University of Minnesota Press.
- Currah, P., & Minter, S. (2000). Unprincipled exclusions: The struggle to achieve judicial and legislative equality for transgender people. *William and Mary Journal of Women and Law*, 7, 37-60.
- Dacakis, G. (2000). Long-term maintenance of fundamental frequency increases in male-to-female transsexuals. *Journal of Voice*, 14(4), 549-556. doi:10.1016/S0892-1997(00)80010-7
- Dahl, M., Feldman, J. L., Goldberg, J. M., & Jaber, A. (2006). Physical aspects of transgender endocrine therapy. *International Journal of Transgenderism*, 9(3), 111-134. doi:10.1300/J485v09n03_06

- Darney, P. D. (2008). Hormonal contraception. In H. M. Kronenberg, S. Melmer, K. S. Polonsky & P. R. Larsen (Eds.), *Williams textbook of endocrinology* (11th ed., pp. 615-644). Philadelphia: Saunders.
- Davies, S., & Goldberg, J. M. (2006). Clinical aspects of transgender speech feminization and masculinization. *International Journal of Transgenderism*, 9(3-4), 167-196. doi:10.1300/J485v09n03_08
- de Bruin, M. D., Coerts, M. J., & Greven, A. J. (2000). Speech therapy in the management of male-to-female transsexuals. *Folia Phoniatica Et Logopaedica*, 52(5), 220-227.
- De Cuypere, G., T'Sjoen, G., Beerten, R., Selvaggi, G., De Sutter, P., Hoebeke, P., . . . Rubens, R. (2005). Sexual and physical health after sex reassignment surgery. *Archives of Sexual Behavior*, 34(6), 679-690. doi:10.1007/s10508-005-7926-5
- De Cuypere, G., Van Hemelrijck, M., Michel, A., Carael, B., Heylens, G., Rubens, R., . . . Monstrey, S. (2007). Prevalence and demography of transsexualism in Belgium. *European Psychiatry*, 22(3), 137-141. doi:10.1016/j.eurpsy.2006.10.002
- De Cuypere, G., & Vercruyse, H. (2009). Eligibility and readiness criteria for sex reassignment surgery: Recommendations for revision of the WPATH standards of care. *International Journal of Transgenderism*, 11(3), 194-205. doi:10.1080/15532730903383781
- de Lignières, B. (1999). Oral micronized progesterone. *Clinical Therapeutics*, 21(1), 41-60. doi:10.1016/S0149-2918(00)88267-3
- De Sutter, P. (2009). Reproductive options for transpeople: Recommendations for revision of the WPATH's standards of care. *International Journal of Transgenderism*, 11(3), 183-185. doi:10.1080/15532730903383765
- De Sutter, P., Kira, K., Verschoor, A., & Hotimsky, A. (2002). The desire to have children and the preservation of fertility in transsexual women: A survey. *International Journal of Transgenderism*, 6(3), retrieved from http://www.wpath.org/journal/www.iiav.nl/ezines/web/IJT/97-03/numbers/symposium/ijtvo06no03_02.htm
- de Vries, A. L. C., Cohen-Kettenis, P. T., & Delemarre-van de Waal, H. A. (2006). Clinical management of gender dysphoria in adolescents. *International Journal of Transgenderism*, 9(3-4), 83-94. doi:10.1300/J485v09n03_04
- de Vries, A. L. C., Doreleijers, T. A. H., Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Psychiatric comorbidity in gender dysphoric adolescents. *Journal of Child Psychology and Psychiatry*. Advance online publication. doi:10.1111/j.1469-7610.2011.02426.x

- de Vries, A. L. C., Noens, I. L. J., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A., & Doreleijers, T. A. (2010). Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders*, 40(8), 930-936. doi:10.1007/s10803-010-0935-9
- de Vries, A. L. C., Steensma, T. D., Doreleijers, T. A. H., & Cohen-Kettenis, P. T. (2010). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *The Journal of Sexual Medicine*. Advance online publication. doi:10.1111/j.1743-6109.2010.01943.x
- Delemarre-van de Waal, H. A., & Cohen-Kettenis, P. T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *European Journal of Endocrinology*, 155(suppl 1), S131-S137. doi:10.1530/eje.1.02231
- Delemarre-van de Waal, H. A., van Weissenbruch, M. M., & Cohen Kettenis, P. T. (2004). Management of puberty in transsexual boys and girls. *Hormone Research in Paediatrics*, 62(suppl 2), 75-75. doi:10.1159/000081145
- Derrig-Palumbo, K., & Zeine, F. (2005). *Online therapy: A therapist's guide to expanding your practice*. New York: W.W. Norton & Co.
- Dessens, A. B., Slijper, F. M. E., & Drop, S. L. S. (2005). Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Archives of Sexual Behavior*, 34(4), 389-397. doi:10.1007/s10508-005-4338-5
- Devor, A. H. (2004). Witnessing and mirroring: A fourteen stage model. *Journal of Gay and Lesbian Psychotherapy*, 8(1/2), 41-67.
- Di Ceglie, D., & Thümmel, E. C. (2006). An experience of group work with parents of children and adolescents with gender identity disorder. *Clinical Child Psychology and Psychiatry*, 11(3), 387-396. doi:10.1177/1359104506064983
- Diamond, M. (2009). Human intersexuality: Difference or disorder? *Archives of Sexual Behavior*, 38(2), 172-172. doi:10.1007/s10508-008-9438-6
- Dobs, A. S., Meikle, A. W., Arver, S., Sanders, S. W., Caramelli, K. E., & Mazer, N. A. (1999). Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *Journal of Clinical Endocrinology & Metabolism*, 84(10), 3469-3478. doi:10.1210/jc.84.10.3469
- Docter, R. F. (1988). *Transvestites and transsexuals: Toward a theory of cross-gender behavior*. New York: Plenum Press.
- Drummond, K. D., Bradley, S. J., Peterson-Badali, M., & Zucker, K. J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology*, 44(1), 34-45. doi:10.1037/0012-1649.44.1.34

- Ehrbar, R. D., & Gorton, R. N. (2010). Exploring provider treatment models in interpreting the standards of care. *International Journal of Transgenderism*, 12(4), 198-2010. doi:10.1080/15532739.2010.544235
- Ekins, R., & King, D. (2006). *The transgender phenomenon*. Thousand Oaks, CA: SAGE Publications Ltd.
- Eklund, P. L., Gooren, L. J., & Bezemer, P. D. (1988). Prevalence of transsexualism in the Netherlands. *British Journal of Psychiatry*, 152(5), 638-640.
- Eldh, J., Berg, A., & Gustafsson, M. (1997). Long-term follow up after sex reassignment surgery. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, 31(1), 39-45.
- Emerson, S., & Rosenfeld, C. (1996). Stages of adjustment in family members of transgender individuals. *Journal of Family Psychotherapy*, 7(3), 1-12. doi:10.1300/J085V07N03_01
- Emory, L. E., Cole, C. M., Avery, E., Meyer, O., & Meyer III, W. J. (2003). Client's view of gender identity: Life, treatment status and outcome. *18th Biennial Harry Benjamin Symposium*, Gent, Belgium.
- Ettner, R., Monstrey, S., & Eyler, A. (Eds.) (2007). *Principles of transgender medicine and surgery*. Binghamton, NY: The Haworth Press.
- Eyler, A. E. (2007). Primary medical care of the gender-variant patient. In R. Ettner, S. Monstrey & E. Eyler (Eds.), *Principles of transgender medicine and surgery* (pp. 15-32). Binghamton, NY: The Haworth Press.
- Factor, R. J., & Rothblum, E. (2008). Exploring gender identity and community among three groups of transgender individuals in the United States: MTFs, FTMs, and genderqueers. *Health Sociology Review*, 17(3), 235-253.
- Feinberg, L. (1996). *Transgender warriors: Making history from Joan of Arc to Dennis Rodman*. Boston, MA: Beacon Press.
- Feldman, J. (2005, April). *Masculinizing hormone therapy with testosterone 1% topical gel*. Paper presented at the 19th Biennial Symposium of the Harry Benjamin International Gender Dysphoria Association, Bologna, Italy.
- Feldman, J. (2007). Preventive care of the transgendered patient. In R. Ettner, S. Monstrey & E. Eyler (Eds.), *Principles of transgender surgery and medicine* (pp. 33-72). Binghamton, NY: The Haworth Press.
- Feldman, J., & Goldberg, J. (2006). Transgender primary medical care. *International Journal of Transgenderism*, 9(3), 3-34. doi:10.1300/J485v09n03_02
- Feldman, J., & Safer, J. (2009). Hormone therapy in adults: Suggested revisions to the sixth version of the standards of care. *International Journal of Transgenderism*, 11(3), 146-182. doi:10.1080/15532730903383757

- Fenichel, M., Suler, J., Barak, A., Zelvin, E., Jones, G., Munro, K., . . . Walker-Schmucker, W. (2004). *Myths and realities of online clinical work, observations on the phenomena of online behavior, experience, and therapeutic relationships. A 3rd-year report from ISMHO's clinical case study group*. Retrieved May 24, 2011, from https://www.ismho.org/myths_n_realities.asp
- Fenway Community Health Transgender Health Program. (2007). *Protocol for hormone therapy*. Retrieved from http://www.fenwayhealth.org/site/DocServer/Fenway_Protocols.pdf?docID=2181
- Fisk, N. M. (1974). Editorial: Gender dysphoria syndrome--the conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen. *Western Journal of Medicine*, 120(5), 386-391.
- Fitzpatrick, L. A., Pace, C., & Wiita, B. (2000). Comparison of regimens containing oral micronized progesterone or medroxyprogesterone acetate on quality of life in postmenopausal women: A cross-sectional survey. *Journal of Women's Health & Gender-Based Medicine*, 9(4), 381-387.
- Frank, J. D., & Frank, J. B. (1993). *Persuasion and healing: A comparative study of psychotherapy* (Third ed.). Baltimore, MD: Johns Hopkins University Press.
- Fraser, L. (2009a). Depth psychotherapy with transgender people. *Sexual and Relationship Therapy*, 24(2), 126-142. doi:10.1080/14681990903003878
- Fraser, L. (2009b). Etherapy: Ethical and clinical considerations for version 7 of The World Professional Association for Transgender Health's standards of care. *International Journal of Transgenderism*, 11(4), 247-263. doi:10.1080/15532730903439492
- Fraser, L. (2009c). Psychotherapy in The World Professional Association for Transgender Health's standards of care: Background and recommendations. *International Journal of Transgenderism*, 11(2), 110-126. doi:10.1080/15532730903008057
- Garaffa, G., Christopher, N. A., & Ralph, D. J. (2010). Total phallic reconstruction in female-to-male transsexuals. *European Urology*, 57(4), 715-722. doi:10.1016/j.eururo.2009.05.018
- Gelder, M. G., & Marks, I. M. (1969). Aversion treatment in transvestism and transsexualism. In R. Green, & J. Money (Eds.), *Transsexualism and sex reassignment* (pp. 383-413). Baltimore, MD: Johns Hopkins Press.
- Gelfer, M. P. (1999). Voice treatment for the male-to-female transgendered client. *American Journal of Speech-Language Pathology*, 8(3), 201-208.
- Gharib, S., Bigby, J., Chapin, M., Ginsburg, E., Johnson, P., Manson, J., & Solomon, C. (2005). *Menopause: A guide to management*. Boston, MA: Brigham and Women's Hospital.

- Gijs, L., & Brewaeys, A. (2007). Surgical treatment of gender dysphoria in adults and adolescents: Recent developments, effectiveness, and challenges. *Annual Review of Sex Research*, 18, 178-224.
- Gold, M., & MacNish, M. (2011). *Adjustment and resiliency following disclosure of transgender identity in families of adolescents and young adults: Themes and clinical implications*. Washington, DC: American Family Therapy Academy.
- Gómez-Gil, E., Trilla, A., Salamero, M., Godás, T., & Valdés, M. (2009). Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Archives of Sexual Behavior*, 38(3), 378-392. doi:10.1007/s10508-007-9307-8
- Gooren, L. (2005). Hormone treatment of the adult transsexual patient. *Hormone Research in Paediatrics*, 64(Suppl 2), 31-36. doi:10.1159/000087751
- Gorton, R. N., Buth, J., & Spade, D. (2005). *Medical therapy and health maintenance for transgender men: A guide for health care providers*. San Francisco, CA: Lyon-Martin Women's Health Services.
- Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
- Green, R., & Fleming, D. (1990). Transsexual surgery follow-up: Status in the 1990s. *Annual Review of Sex Research*, 1(1), 163-174.
- Greenson, R. R. (1964). On homosexuality and gender identity. *International Journal of Psycho-Analysis*, 45, 217-219.
- Grossman, A. H., D'Augelli, A. R., Howell, T. J., & Hubbard, S. (2006). Parent's reactions to transgender youth's gender nonconforming expression and identity. *Journal of Gay & Lesbian Social Services*, 18(1), 3-16. doi:10.1300/J041v18n01_02
- Grossman, A. H., D'Augelli, A. R., & Salter, N. P. (2006). Male-to-female transgender youth: Gender expression milestones, gender atypicality, victimization, and parents' responses. *Journal of GLBT Family Studies*, 2(1), 71-92.
- Grumbach, M. M., Hughes, I. A., & Conte, F. A. (2003). Disorders of sex differentiation. In P. R. Larsen, H. M. Kronenberg, S. Melmed & K. S. Polonsky (Eds.), *Williams textbook of endocrinology* (10th ed., pp. 842-1002). Philadelphia, PA: Saunders.
- Hage, J. J., & De Graaf, F. H. (1993). Addressing the ideal requirements by free flap phalloplasty: Some reflections on refinements of technique. *Microsurgery*, 14(9), 592-598. doi:10.1002/micr.1920140910
- Hage, J. J., & Karim, R. B. (2000). Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plastic and Reconstructive Surgery*, 105(3), 1222-1227.

- Hancock, A. B., Krissinger, J., & Owen, K. (2010). Voice perceptions and quality of life of transgender people. *Journal of Voice*. Advance online publication. doi:10.1016/j.jvoice.2010.07.013
- Hastings, D. W. (1974). Postsurgical adjustment of male transsexual patients. *Clinics in Plastic Surgery*, 1(2), 335-344.
- Hembree, W. C., Cohen-Kettenis, P., Delemarre-van de Waal, H. A., Gooren, L. J., Meyer III, W. J., Spack, N. P., . . . Montori, V. M. (2009). Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 94(9), 3132-3154. doi:10.1210/jc.2009-0345
- Hill, D. B., Menvielle, E., Sica, K. M., & Johnson, A. (2010). An affirmative intervention for families with gender-variant children: Parental ratings of child mental health and gender. *Journal of Sex and Marital Therapy*, 36(1), 6-23. doi:10.1080/00926230903375560
- Hoebeke, P., Selvaggi, G., Ceulemans, P., De Cuypere, G. D., T'Sjoen, G., Weyers, S., . . . Monstrey, S. (2005). Impact of sex reassignment surgery on lower urinary tract function. *European Urology*, 47(3), 398-402. doi:10.1016/j.eururo.2004.10.008
- Hoenig, J., & Kenna, J. C. (1974). The prevalence of transsexualism in England and Wales. *British Journal of Psychiatry*, 124(579), 181-190. doi:10.1192/bjp.124.2.181
- Hughes, I. A., Houk, C. P., Ahmed, S. F., Lee, P. A., & LWPES1/ESPE2 Consensus Group. (2006). Consensus statement on management of intersex disorders. *Archives of Disease in Childhood*, 91(7), 554-563. doi:10.1136/ad.2006.098319
- Hunter, M. H., & Sterrett, J. J. (2000). Polycystic ovary syndrome: It's not just infertility. *American Family Physician*, 62(5), 1079-1095.
- Institute of Medicine. (2011). *The health of lesbian, gay, bisexual, and transgender people: Building a foundation for better understanding*. Washington, DC: The National Academies Press.
- Jackson, P. A., & Sullivan, G. (Eds.). (1999). *Lady boys, tom boys, rent boys: Male and female homosexualities in contemporary Thailand*. Binghamton, NY: The Haworth Press.
- Jockenhövel, F. (2004). Testosterone therapy-what, when and to whom? *The Aging Male*, 7(4), 319-324. doi:10.1080/13685530400016557
- Johansson, A., Sundbom, E., Höjerback, T., & Bodlund, O. (2010). A five-year follow-up study of Swedish adults with gender identity disorder. *Archives of Sexual Behavior*, 39(6), 1429-1437. doi:10.1007/s10508-009-9551-1

- Joint LWPES/ESPE CAH Working Group, Clayton, P. E., Miller, W. L., Oberfield, S. E., Ritzen, E. M., Sippell, W. G., & Speiser, P. W. (2002). Consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology. *Journal of Clinical Endocrinology & Metabolism*, 87(9), 4048-4053. doi:10.1210/jc.2002-020611
- Jurgensen, M., Hiort, O., Holterhus, P. M., & Thyen, U. (2007). Gender role behavior in children with XY karyotype and disorders of sex development. *Hormones and Behavior*, 51(3), 443-453. doi:0.1016/j.yhbeh.2007.01.001
- Kanagalingam, J., Georgalas, C., Wood, G. R., Ahluwalia, S., Sandhu, G., & Cheesman, A. D. (2005). Cricothyroid approximation and subluxation in 21 male-to-female transsexuals. *The Laryngoscope*, 115(4), 611-618. doi:10.1097/01.mlg.0000161357.12826.33
- Kanhai, R. C. J., Hage, J. J., Karim, R. B., & Mulder, J. W. (1999). Exceptional presenting conditions and outcome of augmentation mammoplasty in male-to-female transsexuals. *Annals of Plastic Surgery*, 43(5), 476-483.
- Kimberly, S. (1997). I am transsexual - hear me roar. *Minnesota Law & Politics*, June, 21-49.
- Klein, C., & Gorzalka, B. B. (2009). Sexual functioning in transsexuals following hormone therapy and genital surgery: A review (CME). *The Journal of Sexual Medicine*, 6(11), 2922-2939. doi:10.1111/j.1743-6109.2009.01370.x
- Knudson, G., De Cuypere, G., & Bockting, W. (2010a). Process toward consensus on recommendations for revision of the DSM diagnoses of gender identity disorders by The World Professional Association for Transgender Health. *International Journal of Transgenderism*, 12(2), 54-59. doi:10.1080/15532739.2010.509213
- Knudson, G., De Cuypere, G., & Bockting, W. (2010b). Recommendations for revision of the DSM diagnoses of gender identity disorders: Consensus statement of The World Professional Association for Transgender Health. *International Journal of Transgenderism*, 12(2), 115-118. doi:10.1080/15532739.2010.509215
- Kosilek v. Massachusetts Department of Corrections/Maloney, C.A. No. 92-12820-MLW (U.S. Federal District Court, Boston, MA, 2002).
- Krege, S., Bex, A., Lümmen, G., & Rübber, H. (2001). Male-to-female transsexualism: A technique, results and long-term follow-up in 66 patients. *British Journal of Urology*, 88(4), 396-402. doi:10.1046/j.1464-410X.2001.02323.x

- Kuhn, A., Bodmer, C., Stadlmayr, W., Kuhn, P., Mueller, M. D., & Birkhäuser, M. (2009). Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertility and Sterility*, 92(5), 1685-1689. doi:10.1016/j.fertnstert.2008.08.126
- Kuhn, A., Hildebrand, R., & Birkhauser, M. (2007). Do transsexuals have micturition disorders? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 131(2), 226-230. doi:10.1016/j.ejogrb.2006.03.019
- Landén, M., Wålinder, J., & Lundström, B. (1998). Clinical characteristics of a total cohort of female and male applicants for sex reassignment: A descriptive study. *Acta Psychiatrica Scandinavica*, 97(3), 189-194. doi:10.1111/j.1600-0447.1998.tb09986.x
- Lawrence, A. A. (2003). Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Archives of Sexual Behavior*, 32(4), 299-315. doi:10.1023/A:1024086814364
- Lawrence, A. A. (2006). Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Archives of Sexual Behavior*, 35(6), 717-727. doi:10.1007/s10508-006-9104-9
- Lev, A. I. (2004). *Transgender emergence: Therapeutic guidelines for working with gender-variant people and their families*. Binghamton, NY: Haworth Clinical Practice Press.
- Lev, A. I. (2009). The ten tasks of the mental health provider: Recommendations for revision of The World Professional Association for Transgender Health's standards of care. *International Journal of Transgenderism*, 11(2), 74-99. doi:10.1080/15532730903008032
- Levy, A., Crown, A., & Reid, R. (2003). Endocrine intervention for transsexuals. *Clinical Endocrinology*, 59(4), 409-418. doi:10.1046/j.1365-2265.2003.01821.x
- MacLaughlin, D. T., & Donahoe, P. K. (2004). Sex determination and differentiation. *New England Journal of Medicine*, 350(4), 367-378.
- Maheu, M. M., Pulier, M. L., Wilhelm, F. H., McMenamin, J. P., & Brown-Connolly, N. E. (2005). *The mental health professional and the new technologies: A handbook for practice today*. Mahwah, NJ: Lawrence Erlbaum Associates, Inc.
- Malpas, J. (in press). Between pink and blue: A multi-dimensional family approach to gender nonconforming children and their families. *Family Process*.
- Mazur, T. (2005). Gender dysphoria and gender change in androgen insensitivity or micropenis. *Archives of Sexual Behavior*, 34(4), 411-421. doi:10.1007/s10508-005-4341-x
- McNeill, E. J. M. (2006). Management of the transgender voice. *The Journal of Laryngology & Otology*, 120(07), 521-523. doi:10.1017/S0022215106001174

- McNeill, E. J. M., Wilson, J. A., Clark, S., & Deakin, J. (2008). Perception of voice in the transgender client. *Journal of Voice*, 22(6), 727-733. doi:10.1016/j.jvoice.2006.12.010
- Menvielle, E. J., & Tuerk, C. (2002). A support group for parents of gender-nonconforming boys. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(8), 1010-1013. doi:10.1097/00004583-200208000-00021
- Meyer, I. H. (2003). Prejudice as stress: Conceptual and measurement problems. *American Journal of Public Health*, 93(2), 262-265.
- Meyer, J. K., & Reter, D. J. (1979). Sex reassignment: Follow-up. *Archives of General Psychiatry*, 36(9), 1010-1015.
- Meyer III, W. J. (2009). World Professional Association for Transgender Health's standards of care requirements of hormone therapy for adults with gender identity disorder. *International Journal of Transgenderism*, 11(2), 127-132. doi:10.1080/15532730903008065
- Meyer III, W. J., Webb, A., Stuart, C. A., Finkelstein, J. W., Lawrence, B., & Walker, P. A. (1986). Physical and hormonal evaluation of transsexual patients: A longitudinal study. *Archives of Sexual Behavior*, 15(2), 121-138. doi:10.1007/BF01542220
- Meyer-Bahlburg, H. F. L. (2002). Gender assignment and reassignment in intersexuality: Controversies, data, and guidelines for research. *Advances in Experimental Medicine and Biology*, 511, 199-223. doi:10.1007/978-1-4615-0621-8_12
- Meyer-Bahlburg, H. F. L. (2005). Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Archives of Sexual Behavior*, 34(4), 423-438. doi:10.1007/s10508-005-4342-9
- Meyer-Bahlburg, H. F. L. (2008). Treatment guidelines for children with disorders of sex development. *Neuropsychiatrie De l'Enfance Et De l'Adolescence*, 56(6), 345-349. doi:10.1016/j.neurenf.2008.06.002
- Meyer-Bahlburg, H. F. L. (2009). Variants of gender differentiation in somatic disorders of sex development. *International Journal of Transgenderism*, 11(4), 226-237. doi:10.1080/15532730903439476
- Meyer-Bahlburg, H. F. L. (2010). From mental disorder to iatrogenic hypogonadism: Dilemmas in conceptualizing gender identity variants as psychiatric conditions. *Archives of Sexual Behavior*, 39(2), 461-476. doi:10.1007/s10508-009-9532-4
- Meyer-Bahlburg, H. F. L. (in press). Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child & Adolescent Psychiatric Clinics of North America*.

- Meyer-Bahlburg, H. F. L., & Blizzard, R. M. (2004). Conference proceedings: Research on intersex: Summary of a planning workshop. *The Endocrinologist*, 14(2), 59-69. doi:10.1097/01.ten.0000123701.61007.4e
- Meyer-Bahlburg, H. F. L., Dolezal, C., Baker, S. W., Carlson, A. D., Obeid, J. S., & New, M. I. (2004). Prenatal androgenization affects gender-related behavior but not gender identity in 5–12-year-old girls with congenital adrenal hyperplasia. *Archives of Sexual Behavior*, 33(2), 97-104. doi:10.1023/B:ASEB.0000014324.25718.51
- Meyer-Bahlburg, H. F. L., Dolezal, C., Baker, S. W., Ehrhardt, A. A., & New, M. I. (2006). Gender development in women with congenital adrenal hyperplasia as a function of disorder severity. *Archives of Sexual Behavior*, 35(6), 667-684. doi:10.1007/s10508-006-9068-9
- Meyer-Bahlburg, H. F. L., Migeon, C. J., Berkovitz, G. D., Gearhart, J. P., Dolezal, C., & Wisniewski, A. B. (2004). Attitudes of adult 46,XY intersex persons to clinical management policies. *The Journal of Urology*, 171(4), 1615-1619. doi:10.1097/01.ju.0000117761.94734.b7
- Money, J., & Ehrhardt, A. A. (1972). *Man and woman, boy and girl*. Baltimore, MD: The Johns Hopkins University Press.
- Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role in childhood: Longitudinal follow-up. *Journal of Pediatric Psychology*, 4(1), 29-41. doi:10.1093/jpepsy/4.1.29
- Monstrey, S., Hoebeke, P., Selvaggi, G., Ceulemans, P., Van Landuyt, K., Blondeel, P., . . . De Cuypere, G. (2009). Penile reconstruction: Is the radial forearm flap really the standard technique? *Plastic and Reconstructive Surgery*, 124(2), 510-518.
- Monstrey, S., Selvaggi, G., Ceulemans, P., Van Landuyt, K., Bowman, C., Blondeel, P., . . . De Cuypere, G. (2008). Chest-wall contouring surgery in female-to-male transsexuals: A new algorithm. *Plastic and Reconstructive Surgery*, 121(3), 849-859. doi:10.1097/01.prs.0000299921.15447.b2
- Moore, E., Wisniewski, A., & Dobs, A. (2003). Endocrine treatment of transsexual people: A review of treatment regimens, outcomes, and adverse effects. *Journal of Clinical Endocrinology & Metabolism*, 88(8), 3467-3473. doi:10.1210/jc.2002-021967
- More, S. D. (1998). The pregnant man-an oxymoron? *Journal of Gender Studies*, 7(3), 319-328. doi:10.1080/09589236.1998.9960725
- Mount, K. H., & Salmon, S. J. (1988). Changing the vocal characteristics of a postoperative transsexual patient: A longitudinal study. *Journal of Communication Disorders*, 21(3), 229-238. doi:10.1016/0021-9924(88)90031-7

- Mueller, A., Kiesewetter, F., Binder, H., Beckmann, M. W., & Dittrich, R. (2007). Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. *Journal of Clinical Endocrinology & Metabolism*, 92(9), 3470-3475. doi:10.1210/jc.2007-0746
- Murad, M. H., Elamin, M. B., Garcia, M. Z., Mullan, R. J., Murad, A., Erwin, P. J., & Montori, V. M. (2010). Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clinical Endocrinology*, 72(2), 214-231. doi:10.1111/j.1365-2265.2009.03625.x
- Nanda, S. (1998). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.
- Nestle, J., Wilchins, R. A., & Howell, C. (2002). *Genderqueer: Voices from beyond the sexual binary*. Los Angeles, CA: Alyson Publications.
- Neumann, K., & Welzel, C. (2004). The importance of voice in male-to-female transsexualism. *Journal of Voice*, 18(1), 153-167.
- Newfield, E., Hart, S., Dibble, S., & Kohler, L. (2006). Female-to-male transgender quality of life. *Quality of Life Research*, 15(9), 1447-1457. doi:10.1007/s11136-006-0002-3
- Nieschlag, E., Behre, H. M., Bouchard, P., Corrales, J. J., Jones, T. H., Stalla, G. K., . . . Wu, F. C. W. (2004). Testosterone replacement therapy: Current trends and future directions. *Human Reproduction Update*, 10(5), 409-419. doi:10.1093/humupd/dmh035
- North American Menopause Society. (2010). Estrogen and progestogen use in postmenopausal women: 2010 position statement. *Menopause*, 17(2), 242-255. doi:10.1097/gme.0b013e3181d0f6b9
- Nuttbrock, L., Hwahng, S., Bockting, W., Rosenblum, A., Mason, M., Macri, M., & Becker, J. (2010). Psychiatric impact of gender-related abuse across the life course of male-to-female transgender persons. *Journal of Sex Research*, 47(1), 12-23. doi:10.1080/00224490903062258
- Oates, J. M., & Dacakis, G. (1983). Speech pathology considerations in the management of transsexualism-a review. *International Journal of Language & Communication Disorders*, 18(3), 139-151. doi:10.3109/13682828309012237
- Olyslager, F., & Conway, L. (2007). On the calculation of the prevalence of transsexualism. Paper presented at the *World Professional Association for Transgender Health 20th International Symposium*, Chicago, Illinois. Retrieved April 22, 2010 from http://www.changelingaspects.com/PDF/2007-09-06-Prevalence_of_Transsexualism.pdf

- Oriel, K. A. (2000). Clinical update: Medical care of transsexual patients. *Journal of the Gay and Lesbian Medical Association*, 4(4), 185-194. doi:1090-7173/00/1200-0185\$18.00/1
- Pauly, I. B. (1965). Male psychosexual inversion: Transsexualism: A review of 100 cases. *Archives of General Psychiatry*, 13(2), 172-181.
- Payer, A. F., Meyer III, W. J., & Walker, P. A. (1979). The ultrastructural response of human leydig cells to exogenous estrogens. *Andrologia*, 11(6), 423-436. doi:10.1111/j.1439-0272.1979.tb02232.x
- Peletz, M. G. (2006). Transgenderism and gender pluralism in southeast asia since early modern times. *Current Anthropology*, 47(2), 309-340. doi:10.1086/498947
- Pfäfflin, F. (1993). Regrets after sex reassignment surgery. *Journal of Psychology & Human Sexuality*, 5(4), 69-85.
- Pfäfflin, F., & Junge, A. (1998). Sex reassignment. Thirty years of international follow-up studies after sex reassignment surgery: A comprehensive review, 1961-1991. *International Journal of Transgenderism*. Retrieved from <http://web.archive.org/web/20070503090247/http://www.symposion.com/ijt/pfaefflin/1000.htm>
- Physicians' desk reference*. (61st ed.). (2007). Montvale, NJ: PDR.
- Physicians' desk reference*. (65th ed.). (2010). Montvale, NJ: PDR.
- Pleak, R. R. (1999). Ethical issues in diagnosing and treating gender-dysphoric children and adolescents. In M. Rottnek (Ed.), *Sissies and tomboys: Gender nonconformity and homosexual childhood* (pp. 34-51). New York: New York University Press.
- Pope, K. S., & Vasquez, M. J. (2011). *Ethics in psychotherapy and counseling: A practical guide* (Fourth ed.). Hoboken, NJ: John Wiley & Sons, Inc.
- Prior, J. C., Vigna, Y. M., & Watson, D. (1989). Spironolactone with physiological female steroids for presurgical therapy of male-to-female transsexualism. *Archives of Sexual Behavior*, 18(1), 49-57. doi:10.1007/BF01579291
- Prior, J. C., Vigna, Y. M., Watson, D., Diewold, P., & Robinow, O. (1986). Spironolactone in the presurgical therapy of male to female transsexuals: Philosophy and experience of the Vancouver Gender Dysphoria Clinic. *Journal of Sex Information & Education Council of Canada*, 1, 1-7.
- Rachlin, K. (1999). Factors which influence individual's decisions when considering female-to-male genital reconstructive surgery. *International Journal of Transgenderism*, 3(3). Retrieved from <http://www.WPATH.org>

- Rachlin, K. (2002). Transgendered individuals' experiences of psychotherapy. *International Journal of Transgenderism*, 6(1). Retrieved from http://www.wpath.org/journal/www.iiv.nl/eazines/web/IJT/97-03/numbers/symposium/ijtv06no01_03.htm.
- Rachlin, K., Green, J., & Lombardi, E. (2008). Utilization of health care among female-to-male transgender individuals in the United States. *Journal of Homosexuality*, 54(3), 243-258. doi:10.1080/00918360801982124
- Rachlin, K., Hansbury, G., & Pardo, S. T. (2010). Hysterectomy and oophorectomy experiences of female-to-male transgender individuals. *International Journal of Transgenderism*, 12(3), 155-166. doi:10.1080/15532739.2010.514220
- Reed, B., Rhodes, S., Schofield, P. & Wylie, K. (2009). *Gender variance in the UK: Prevalence, incidence, growth and geographic distribution*. Retrieved June 8, 2011, from <http://www.gires.org.uk/assets/Medpro-Assets/GenderVarianceUK-report.pdf>
- Rehman, J., Lazer, S., Benet, A. E., Schaefer, L. C., & Melman, A. (1999). The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Archives of Sexual Behavior*, 28(1), 71-89. doi:10.1023/A:1018745706354
- Robinow, O. (2009). Paraphilia and transgenderism: A connection with Asperger's disorder? *Sexual and Relationship Therapy*, 24(2), 143-151. doi:10.1080/14681990902951358
- Rosenberg, M. (2002). Children with gender identity issues and their parents in individual and group treatment. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41(5), 619-621. doi:10.1097/00004583-200205000-00020
- Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Kooperberg, C., Stefanick, M. L., . . . Johnson, K. C. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the women's health initiative randomized controlled trial. *JAMA: The Journal of the American Medical Association*, 288(3), 321-333.
- Royal College of Speech Therapists, United Kingdom. <http://www.rcslt.org/>
- Ruble, D. N., Martin, C. L., & Berenbaum, S. A. (2006). Gender development. In N. Eisenberg, W. Damon & R. M. Lerner (Eds.), *Handbook of child psychology* (6th ed., pp. 858-932). Hoboken, NJ: John Wiley & Sons, Inc.
- Sausa, L. A. (2005). Translating research into practice: Trans youth recommendations for improving school systems. *Journal of Gay & Lesbian Issues in Education*, 3(1), 15-28. doi:10.1300/J367v03n01_04
- Simpson, J. L., de la Cruz, F., Swerdloff, R. S., Samango-Sprouse, C., Skakkebaek, N. E., Graham, J. M. J., . . . Willard, H. F. (2003). Klinefelter syndrome: Expanding the phenotype and identifying new research directions. *Genetics in Medicine*, 5(6), 460-468. doi:10.1097/01.GIM.0000095626.54201.DO

- Smith, Y. L. S., Van Goozen, S. H. M., Kuiper, A. J., & Cohen-Kettenis, P. T. (2005). Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychological Medicine*, 35(1), 89-99. doi:10.1017/S0033291704002776
- Sood, R., Shuster, L., Smith, R., Vincent, A., & Jatoi, A. (2011). Counseling postmenopausal women about bioidentical hormones: Ten discussion points for practicing physicians. *Journal of the American Board of Family Practice*, 24(2), 202-210. doi:10.3122/jabfm.2011.02.100194
- Speech Pathology Australia. <http://www.speechpathologyaustralia.org.au/>
- Speiser, P. W., Azziz, R., Baskin, L. S., Ghizzoni, L., Hensle, T. W., Merke, D. P., . . . Oberfield, S. E. (2010). Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism*, 95(9), 4133-4160. doi:10.1210/jc.2009-2631
- Steensma, T. D., Biemond, R., de Boer, F., & Cohen-Kettenis, P. T. (2011). Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clinical Child Psychology and Psychiatry*. Advance online publication. doi:10.1177/1359104510378303
- Steensma, T. D., & Cohen-Kettenis, P. T. (2011). Gender transitioning before puberty? *Archives of Sexual Behavior*, 40(4), 649-650. doi:10.1007/s10508-011-9752-2
- Stikkelbroeck, N. M. M. L., Beerendonk, C., Willemssen, W. N. P., Schreuders-Bais, C. A., Feitz, W. F. J., Rieu, P. N. M. A., . . . Otten, B. J. (2003). The long term outcome of feminizing genital surgery for congenital adrenal hyperplasia: Anatomical, functional and cosmetic outcomes, psychosexual development, and satisfaction in adult female patients. *Journal of Pediatric and Adolescent Gynecology*, 16(5), 289-296. doi:10.1016/S1083-3188(03)00155-4
- Stoller, R. J. (1964). A contribution to the study of gender identity. *International Journal of Psychoanalysis*, 45, 220-226.
- Stone, S. (1991). The empire strikes back: A posttranssexual manifesto. In J. Epstein, & K. Straub (Eds.), *Body guards: The cultural politics of gender ambiguity* (pp. 280-304). London: Routledge.
- Tangpricha, V., Ducharme, S. H., Barber, T. W., & Chipkin, S. R. (2003). Endocrinologic treatment of gender identity disorders. *Endocrine Practice*, 9(1), 12-21.
- Tangpricha, V., Turner, A., Malabanan, A., & Holick, M. (2001). Effects of testosterone therapy on bone mineral density in the FTM patient. *International Journal of Transgenderism*, 5(4).
- Taywaditep, K. J., Coleman, E., & Dumronggittigule, P. (1997). Thailand (muang thai). In R. Francouer (Ed.), *International encyclopedia of sexuality*. New York: Continuum.

- The World Professional Association for Transgender Health, Inc. (2008). *WPATH clarification on medical necessity of treatment, sex reassignment, and insurance coverage in the U.S.A.* Retrieved from <http://www.wpath.org/documents/Med%20Nec%20on%202008%20Letterhead.pdf>
- Thole, Z., Manso, G., Salgueiro, E., Revuelta, P., & Hidalgo, A. (2004). Hepatotoxicity induced by antiandrogens: A review of the literature. *Urologia Internationalis*, 73(4), 289-295. doi:10.1159/000081585
- Tom Waddell Health Center. (2006). *Protocols for hormonal reassignment of gender*. Retrieved from <http://www.sfdph.org/dph/comupg/oservices/medSvs/hlthCtrs/TransGendprotocols122006.pdf>
- Tsoi, W. F. (1988). The prevalence of transsexualism in Singapore. *Acta Psychiatrica Scandinavica*, 78(4), 501-504. doi:10.1111/j.1600-0447.1988.tb06373.x
- Van den Broecke, R., Van der Elst, J., Liu, J., Hovatta, O., & Dhont, M. (2001). The female-to-male transsexual patient: A source of human ovarian cortical tissue for experimental use. *Human Reproduction*, 16(1), 145-147. doi:10.1093/humrep/16.1.145
- van Kesteren, P. J. M., Asscheman, H., Megens, J. A. J., & Gooren, L. J. G. (1997). Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clinical Endocrinology*, 47(3), 337-343. doi:10.1046/j.1365-2265.1997.2601068.x
- van Kesteren, P. J. M., Gooren, L. J., & Megens, J. A. (1996). An epidemiological and demographic study of transsexuals in the Netherlands. *Archives of Sexual Behavior*, 25(6), 589-600. doi:10.1007/BF02437841
- van Trotsenburg, M. A. A. (2009). Gynecological aspects of transgender healthcare. *International Journal of Transgenderism*, 11(4), 238-246. doi:10.1080/15532730903439484
- Vancouver Coastal Health, Vancouver, British Columbia, Canada. <http://www.vch.ca/>
- Vanderburgh, R. (2009). Appropriate therapeutic care for families with pre-pubescent transgender/gender-dissonant children. *Child and Adolescent Social Work Journal*, 26(2), 135-154. doi:10.1007/s10560-008-0158-5
- Vilain, E. (2000). Genetics of sexual development. *Annual Review of Sex Research*, 11, 1-25.
- Wålinder, J. (1968). Transsexualism: Definition, prevalence and sex distribution. *Acta Psychiatrica Scandinavica*, 43(S203), 255-257.
- Wålinder, J. (1971). Incidence and sex ratio of transsexualism in Sweden. *The British Journal of Psychiatry*, 119(549), 195-196.
- Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(12), 1413-1423. doi:10.1097/CHI.0b013e31818956b9

- Wallien, M. S. C., Swaab, H., & Cohen-Kettenis, P. T. (2007). Psychiatric comorbidity among children with gender identity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46(10), 1307-1314. doi:10.1097/chi.0b013e3181373848
- Warren, B. E. (1993). Transsexuality, identity and empowerment. A view from the frontlines. *SIECUS Report*, February/March, 14-16.
- Weitze, C., & Osburg, S. (1996). Transsexualism in Germany: Empirical data on epidemiology and application of the German Transsexuals' Act during its first ten years. *Archives of Sexual Behavior*, 25(4), 409-425.
- Wilson, J. D. (1999). The role of androgens in male gender role behavior. *Endocrine Reviews*, 20(5), 726-737. doi:10.1210/er.20.5.726
- Winter, S. (2009). Cultural considerations for The World Professional Association for Transgender Health's standards of care: The Asian perspective. *International Journal of Transgenderism*, 11(1), 19-41. doi:10.1080/15532730902799938
- Winter, S., Chalungsooth, P., Teh, Y. K., Rojanalert, N., Maneerat, K., Wong, Y. W., . . . Macapagal, R. A. (2009). Transpeople, transprejudice and pathologization: A seven-country factor analytic study. *International Journal of Sexual Health*, 21(2), 96-118. doi:10.1080/19317610902922537
- Wisniewski, A. B., Migeon, C. J., Malouf, M. A., & Gearhart, J. P. (2004). Psychosexual outcome in women affected by congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *The Journal of Urology*, 171(6, Part 1), 2497-2501. doi:10.1097/01.ju.0000125269.91938.f7
- World Health Organization. (2007). *International classification of diseases and related health problems-10th revision*. Geneva, Switzerland: World Health Organization.
- World Health Organization. (2008). *The world health report 2008: Primary health care - now more than ever*. Geneva, Switzerland: World Health Organization.
- WPATH Board of Directors. (2010). *De-psychopathologisation statement released May 26, 2010*. Retrieved from http://wpath.org/announcements_detail.cfm?pk_announcement=17
- Xavier, J. M. (2000). *The Washington, D.C. transgender needs assessment survey: Final report for phase two*. Washington, DC: Administration for HIV/AIDS of District of Columbia Government.
- Zhang, G., Gu, Y., Wang, X., Cui, Y., & Bremner, W. J. (1999). A clinical trial of injectable testosterone undecanoate as a potential male contraceptive in normal Chinese men. *Journal of Clinical Endocrinology & Metabolism*, 84(10), 3642-3647. doi:10.1210/jc.84.10.3642

- Zitzmann, M., Saad, F., & Nieschlag, E. (2006, April). *Long term experience of more than 8 years with a novel formulation of testosterone undecanoate (nebido) in substitution therapy of hypogonadal men*. Paper presented at European Congress of Endocrinology, Glasgow, UK, April 2006.
- Zucker, K. J. (1999). Intersexuality and gender identity differentiation. *Annual Review of Sex Research*, 10(1), 1-69.
- Zucker, K. J. (2004). Gender identity development and issues. *Child and Adolescent Psychiatric Clinics of North America*, 13(3), 551-568. doi:10.1016/j.chc.2004.02.006
- Zucker, K. J. (2006). 'I'm half-boy, half-girl': Play psychotherapy and parent counseling for gender identity disorder. In R. L. Spitzer, M. B. First, J. B. W. Williams & M. Gibbons (Eds.), *DSM-IV-TR casebook, volume 2* (pp. 321-334). Arlington, VA: American Psychiatric Publishing, Inc.
- Zucker, K. J. (2010). The DSM diagnostic criteria for gender identity disorder in children. *Archives of Sexual Behavior*, 39(2), 477-498. doi:10.1007/s10508-009-9540-4
- Zucker, K. J., & Bradley, S. J. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York: Guilford Press.
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., & Cantor, J. M. (2008). Is gender identity disorder in adolescents coming out of the closet? *Journal of Sex & Marital Therapy*, 34(4), 287-290. doi:10.1080/00926230802096192
- Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., Wood, H., Singh, D., & Choi, K. (in press). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex & Marital Therapy*.
- Zucker, K. J., & Lawrence, A. A. (2009). Epidemiology of gender identity disorder: Recommendations for the standards of care of The World Professional Association for Transgender Health. *International Journal of Transgenderism*, 11(1), 8-18. doi:10.1080/15532730902799946
- Zucker, K. J., Owen, A., Bradley, S. J., & Ameeriar, L. (2002). Gender-dysphoric children and adolescents: A comparative analysis of demographic characteristics and behavioral problems. *Clinical Child Psychology and Psychiatry*, 7(3), 398-411.
- Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease*, 172(2), 90-97.

APPENDIX A

GLOSSARY

Terminology in the area of health care for transsexual, transgender, and gender nonconforming people is rapidly evolving; new terms are being introduced, and the definitions of existing terms are changing. Thus, there is often misunderstanding, debate, or disagreement about language in this field. Terms that may be unfamiliar or that have specific meanings in the SOC are defined below for the purpose of this document only. Others may adopt these definitions, but WPATH acknowledges that these terms may be defined differently in different cultures, communities, and contexts.

WPATH also acknowledges that many terms used in relation to this population are not ideal. For example, the terms *transsexual* and *transvestite* – and, some would argue, the more recent term *transgender* – have been applied to people in an objectifying fashion. Yet such terms have been more or less adopted by many people who are making their best effort to make themselves understood. By continuing to use these terms, WPATH intends only to ensure that concepts and processes are comprehensible, in order to facilitate the delivery of quality health care to transsexual, transgender, and gender nonconforming people. WPATH remains open to new terminology that will further illuminate the experience of members of this diverse population and lead to improvements in health care access and delivery.

Bioidentical hormones: Hormones that are *structurally* identical to those found in the human body (ACOG Committee of Gynecologic Practice, 2005). The hormones used in bioidentical hormone therapy (BHT) are generally derived from plant sources and are structurally similar to endogenous human hormones, but they need to be commercially processed to become bioidentical.

Bioidentical compounded hormone therapy (BCHT): Use of hormones that are prepared, mixed, assembled, packaged, or labeled as a drug by a pharmacist and custom-made for a patient according to a physician’s specifications. Government drug agency approval is not possible for each compounded product made for an individual consumer.

Crossdressing (transvestism): Wearing clothing and adopting a gender role presentation that, in a given culture, is more typical of the other sex.

Disorders of sex development (DSD): Congenital conditions in which the development of chromosomal, gonadal, or anatomic sex is atypical. Some people strongly object to the “disorder” label and instead view these conditions as a matter of diversity (Diamond, 2009), preferring the terms *intersex* and *intersexuality*.

Female-to-Male (FtM): Adjective to describe individuals assigned female at birth who are changing or who have changed their body and/or gender role from birth-assigned female to a more masculine body or role.

Gender dysphoria: Distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b).

Gender identity: A person's intrinsic sense of being male (a boy or a man), female (a girl or woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch) (Bockting, 1999; Stoller, 1964).

Gender identity disorder: Formal diagnosis set forth by the *Diagnostic Statistical Manual of Mental Disorders, 4th Edition, Text Rev (DSM IV-TR)* (American Psychiatric Association, 2000). Gender identity disorder is characterized by a strong and persistent cross-gender identification and a persistent discomfort with one's sex or sense of inappropriateness in the gender role of that sex, causing clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Gender nonconforming: Adjective to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period.

Gender role or expression: Characteristics in personality, appearance, and behavior that in a given culture and historical period are designated as masculine or feminine (that is, more typical of the male or female social role) (Ruble, Martin, & Berenbaum, 2006). While most individuals present socially in clearly male or female gender roles, some people present in an alternative gender role such as genderqueer or specifically transgender. All people tend to incorporate both masculine and feminine characteristics in their gender expression in varying ways and to varying degrees (Bockting, 2008).

Genderqueer: Identity label that may be used by individuals whose gender identity and/or role does not conform to a binary understanding of gender as limited to the categories of man or woman, male or female (Bockting, 2008).

Male-to-Female (MtF): Adjective to describe individuals assigned male at birth who are changing or who have changed their body and/or gender role from birth-assigned male to a more feminine body or role.

Natural hormones: Hormones that are derived from natural *sources* such as plants or animals. Natural hormones may or may not be bioidentical.

Sex: Sex is assigned at birth as male or female, usually based on the appearance of the external genitalia. When the external genitalia are ambiguous, other components of sex (internal genitalia, chromosomal and hormonal sex) are considered in order to assign sex (Grumbach, Hughes, & Conte,

2003; MacLaughlin & Donahoe, 2004; Money & Ehrhardt, 1972; Vilain, 2000). For most people, gender identity and expression are consistent with their sex assigned at birth; for transsexual, transgender, and gender nonconforming individuals, gender identity or expression differ from their sex assigned at birth.

Sex reassignment surgery (gender affirmation surgery): Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity. Sex reassignment surgery can be an important part of medically necessary treatment to alleviate gender dysphoria.

Transgender: Adjective to describe a diverse group of individuals who cross or transcend culturally-defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth (Bockting, 1999).

Transition: Period of time when individuals change from the gender role associated with their sex assigned at birth to a different gender role. For many people, this involves learning how to live socially in "the other" gender role; for others this means finding a gender role and expression that is most comfortable for them. Transition may or may not include feminization or masculinization of the body through hormones or other medical procedures. The nature and duration of transition is variable and individualized.

Transphobia, internalized: Discomfort with one's own transgender feelings or identity as a result of internalizing society's normative gender expectations.

Transsexual: Adjective (often applied by the medical profession) to describe individuals who seek to change or who have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role.

APPENDIX B

OVERVIEW OF MEDICAL RISKS OF HORMONE THERAPY

The risks outlined below are based on two comprehensive, evidence-based literature reviews of masculinizing/feminizing hormone therapy (Feldman & Safer, 2009; Hembree et al., 2009), along with a large cohort study (Asscheman et al., 2011). These reviews can serve as detailed references for providers, along with other widely recognized, published clinical materials (e.g., Dahl et al., 2006; Ettner et al., 2007).

Risks of Feminizing Hormone Therapy (MtF)

Likely increased risk:

Venous thromboembolic disease

- Estrogen use increases the risk of venous thromboembolic events (VTE), particularly in patients who are over age 40, smokers, highly sedentary, obese, and who have underlying thrombophilic disorders.
- This risk is increased with the additional use of third generation progestins.
- This risk is decreased with use of the transdermal route of estradiol administration, which is recommended for patients at higher risk of VTE.

Cardiovascular, cerebrovascular disease

- Estrogen use increases the risk of cardiovascular events in patients over age 50 with underlying cardiovascular risk factors. Additional progestin use may increase this risk.

Lipids

- Oral estrogen use may markedly increase triglycerides in patients, increasing the risk of pancreatitis and cardiovascular events.
- Different routes of administration will have different metabolic effects on levels of HDL cholesterol, LDL cholesterol and lipoprotein(a).
- In general, clinical evidence suggests that MtF patients with pre-existing lipid disorders may benefit from the use of transdermal rather than oral estrogen.

Liver/gallbladder

- Estrogen and cyproterone acetate use may be associated with transient liver enzyme elevations and, rarely, clinical hepatotoxicity.
- Estrogen use increases the risk of cholelithiasis (gall stones) and subsequent cholecystectomy.

Possible increased risk:

Type 2 diabetes mellitus

- Feminizing hormone therapy, particularly estrogen, may increase the risk of type 2 diabetes, particularly among patients with a family history of diabetes or other risk factors for this disease.

Hypertension

- Estrogen use may increase blood pressure, but the effect on incidence of overt hypertension is unknown.
- Spironolactone reduces blood pressure and is recommended for at-risk or hypertensive patients desiring feminization.

Prolactinoma

- Estrogen use increases the risk of hyperprolactinemia among MtF patients in the first year of treatment, but this risk unlikely thereafter.
- High-dose estrogen use may promote the clinical appearance of preexisting but clinically unapparent prolactinoma.

Inconclusive or no increased risk: Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Breast cancer

- MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia.
- Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk.

Other side effects of feminizing therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with feminizing hormone therapy.

Fertility and sexual function

- Feminizing hormone therapy may impair fertility.
- Feminizing hormone therapy may decrease libido.
- Feminizing hormone therapy reduces nocturnal erections, with variable impact on sexually stimulated erections.

Risks of anti-androgen medications:

Feminizing hormone regimens often include a variety of agents that affect testosterone production or action. These include GnRH agonists, progestins (including cyproterone acetate), spironolactone, and 5-alpha reductase inhibitors. An extensive discussion of the specific risks of these agents is beyond the scope of the SOC. However, both spironolactone and cyproterone acetate are widely used and deserve some comment.

Cyproterone acetate is a progestational compound with anti-androgenic properties (Gooren, 2005; Levy et al., 2003). Although widely used in Europe, it is not approved for use in the United States because of concerns about hepatotoxicity (Thole, Manso, Salgueiro, Revuelta, & Hidalgo, 2004). Spironolactone is commonly used as an anti-androgen in feminizing hormone therapy, particularly in regions where cyproterone is not approved for use (Dahl et al., 2006; Moore et al., 2003; Tangpricha et al., 2003). Spironolactone has a long history of use in treating hypertension and congestive heart failure. Its common side effects include hyperkalemia, dizziness, and gastrointestinal symptoms (*Physicians' Desk Reference*, 2007).

Risks of Masculinizing Hormone Therapy (FtM)

Likely increased risk:

Polycythemia

- Masculinizing hormone therapy involving testosterone or other androgenic steroids increases the risk of polycythemia (hematocrit > 50%), particularly in patients with other risk factors.
- Transdermal administration and adaptation of dosage may reduce this risk

Weight gain/visceral fat

- Masculinizing hormone therapy can result in modest weight gain, with an increase in visceral fat.

Possible increased risk:

Lipids

- Testosterone therapy decreases HDL, but variably affects LDL and triglycerides.
- Supraphysiologic (beyond normal male range) serum levels of testosterone, often found with extended intramuscular dosing, may worsen lipid profiles, whereas transdermal administration appears to be more lipid neutral.
- Patients with underlying polycystic ovarian syndrome or dyslipidemia may be at increased risk of worsening dyslipidemia with testosterone therapy.

Liver

- Transient elevations in liver enzymes may occur with testosterone therapy.
- Hepatic dysfunction and malignancies have been noted with oral methyltestosterone. However, methyltestosterone is no longer available in most countries and should no longer be used.

Psychiatric

Masculinizing therapy involving testosterone or other androgenic steroids may increase the risk of hypomanic, manic, or psychotic symptoms in patients with underlying psychiatric disorders that include such symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone

Inconclusive or no increased risk: Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among FtM patients prior to oophorectomy, at least in the first three years of treatment.
- There is an increased risk of bone density loss after oophorectomy, particularly if testosterone therapy is interrupted or insufficient. This includes patients utilizing solely oral testosterone.

Cardiovascular

- Masculinizing hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinizing hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

Hypertension

- Masculinizing hormone therapy at normal physiologic doses may increase blood pressure but does not appear to increase the risk of hypertension.
- Patients with risk factors for hypertension, such as weight gain, family history, or polycystic ovarian syndrome, may be at increased risk.

Type 2 diabetes mellitus

- Testosterone therapy does not appear to increase the risk of type 2 diabetes among FtM patients overall.

- Testosterone therapy may further increase the risk of type 2 diabetes in patients with other risk factors, such as significant weight gain, family history, and polycystic ovarian syndrome. There are no data that suggest or show an increase in risk in those with risk factors for dyslipidemia.

Breast cancer

- Testosterone therapy in FtM patients does not increase the risk of breast cancer.

Cervical cancer

- Testosterone therapy in FtM patients does not increase the risk of cervical cancer, although it may increase the risk of minimally abnormal Pap smears due to atrophic changes.

Ovarian cancer

- Analogous to persons born with female genitalia with elevated androgen levels, testosterone therapy in FtM patients may increase the risk of ovarian cancer, although evidence is limited.

Endometrial (uterine) cancer

- Testosterone therapy in FtM patients may increase the risk of endometrial cancer, although evidence is limited.

Other side effects of masculinizing therapy:

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with masculinization.

Fertility and sexual function

- Testosterone therapy in FtM patients reduces fertility, although the degree and reversibility are unknown.
- Testosterone therapy can induce permanent anatomic changes in the developing embryo or fetus.
- Testosterone therapy induces clitoral enlargement and increases libido.

Acne, androgenic alopecia

Acne and varying degrees of male pattern hair loss (androgenic alopecia) are common side effects of masculinizing hormone therapy.

APPENDIX C

SUMMARY OF CRITERIA FOR HORMONE THERAPY AND SURGERIES

As for all previous versions of the SOC, the criteria put forth in the SOC for hormone therapy and surgical treatments for gender dysphoria are clinical guidelines; individual health professionals and programs may modify them. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm reduction strategies. These departures should be recognized as such, explained to the patient, and documented through informed consent for quality patient care and legal protection. This documentation is also valuable to accumulate new data, which can be retrospectively examined to allow for health care – and the SOC – to evolve.

Criteria for Feminizing/Masculinizing Hormone Therapy (one referral or chart documentation of psychosocial assessment)

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental concerns are present, they must be reasonably well-controlled.

Criteria for Breast/Chest Surgery (one referral)

Mastectomy and creation of a male chest in FtM patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormone therapy is not a pre-requisite.

Breast augmentation (implants/lipofilling) in MtF patients:

1. Persistent, well-documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country (if younger, follow the SOC for children and adolescents);
4. If significant medical or mental health concerns are present, they must be reasonably well controlled.

Although not an explicit criterion, it is recommended that MtF patients undergo feminizing hormone therapy (minimum 12 months) prior to breast augmentation surgery. The purpose is to maximize breast growth in order to obtain better surgical (aesthetic) results.

Criteria for genital surgery (two referrals)

Hysterectomy and ovariectomy in FtM patients and orchiectomy in MtF patients:

1. Persistent, well documented gender dysphoria;

2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).

The aim of hormone therapy prior to gonadectomy is primarily to introduce a period of reversible estrogen or testosterone suppression, before a patient undergoes irreversible surgical intervention.

These criteria do not apply to patients who are having these surgical procedures for medical indications other than gender dysphoria.

Metoidioplasty or phalloplasty in FtM patients and vaginoplasty in MtF patients:

1. Persistent, well documented gender dysphoria;
2. Capacity to make a fully informed decision and to consent for treatment;
3. Age of majority in a given country;
4. If significant medical or mental health concerns are present, they must be well controlled;
5. 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones);
6. 12 continuous months of living in a gender role that is congruent with their gender identity.

Although not an explicit criterion, it is recommended that these patients also have regular visits with a mental health or other medical professional.

The criterion noted above for some types of genital surgeries – i.e., that patients engage in 12 continuous months of living in a gender role that is congruent with their gender identity – is based on expert clinical consensus that this experience provides ample opportunity for patients to experience and socially adjust in their desired gender role, before undergoing irreversible surgery.

APPENDIX D

EVIDENCE FOR CLINICAL OUTCOMES OF THERAPEUTIC APPROACHES

One of the real supports for any new therapy is an outcome analysis. Because of the controversial nature of sex reassignment surgery, this type of analysis has been very important. Almost all of the outcome studies in this area have been retrospective.

One of the first studies to examine the post-treatment psychosocial outcomes of transsexual patients was done in 1979 at Johns Hopkins University School of Medicine and Hospital (USA) (J. K. Meyer & Reter, 1979). This study focused on patients' occupational, educational, marital, and domiciliary stability. The results revealed several significant changes with treatment. These changes were not seen as positive; rather, they showed that many individuals who had entered the treatment program were no better off or were worse off in many measures after participation in the program. These findings resulted in closure of the treatment program at that hospital/medical school (Abramowitz, 1986).

Subsequently, a significant number of health professionals called for a standard for eligibility for sex reassignment surgery. This led to the formulation of the original *Standards of Care* of the Harry Benjamin International Gender Dysphoria Association (now WPATH) in 1979.

In 1981, Pauly published results from a large retrospective study of people who underwent sex reassignment surgery. Participants in that study had much better outcomes: Among 83 FtM patients, 80.7% had a satisfactory outcome (i.e., patient self report of "improved social and emotional adjustment"), 6.0% unsatisfactory. Among 283 MtF patients, 71.4% had a satisfactory outcome, 8.1% unsatisfactory. This study included patients who were treated before the publication and use of the *Standards of Care*.

Since the *Standards of Care* have been in place, there has been a steady increase in patient satisfaction and decrease in dissatisfaction with the outcome of sex reassignment surgery. Studies conducted after 1996 focused on patients who were treated according to the *Standards of Care*. The findings of Rehman and colleagues (1999) and Krege and colleagues (2001) are typical of this body of work; none of the patients in these studies regretted having had surgery, and most reported being satisfied with the cosmetic and functional results of the surgery. Even patients who develop severe surgical complications seldom regret having undergone surgery. Quality of surgical results is one of the best predictors of the overall outcome of sex reassignment (Lawrence, 2003). The vast majority of follow-up studies have shown an undeniable beneficial effect of sex reassignment surgery on postoperative outcomes such as subjective well being, cosmesis, and sexual function (De Cuypere et al., 2005; Garaffa, Christopher, & Ralph, 2010; Klein & Gorzalka, 2009), although the specific magnitude of benefit is uncertain from

the currently available evidence. One study (Emory, Cole, Avery, Meyer, & Meyer III, 2003) even showed improvement in patient income.

One troubling report (Newfield et al., 2006) documented lower scores on quality of life (measured with the SF-36) for FtM patients than for the general population. A weakness of that study is that it recruited its 384 participants by a general email rather than a systematic approach, and the degree and type of treatment was not recorded. Study participants who were taking testosterone had typically been doing so for less than 5 years. Reported quality of life was higher for patients who had undergone breast/chest surgery than for those who had not ($p < .001$). (A similar analysis was not done for genital surgery). In other work, Kuhn and colleagues (2009) used the King's Health Questionnaire to assess the quality of life of 55 transsexual patients at 15 years after surgery. Scores were compared to those of 20 healthy female control patients who had undergone abdominal/pelvic surgery in the past. Quality of life scores for transsexual patients were the same or better than those of control patients for some subscales (emotions, sleep, incontinence, symptom severity, and role limitation), but worse in other domains (general health, physical limitation, and personal limitation).

It is difficult to determine the effectiveness of hormones alone in the relief of gender dysphoria. Most studies evaluating the effectiveness of masculinizing/feminizing hormone therapy on gender dysphoria have been conducted with patients who have also undergone sex reassignment surgery. Favorable effects of therapies that included both hormones and surgery were reported in a comprehensive review of over 2000 patients in 79 studies (mostly observational) conducted between 1961 and 1991 (Eldh, Berg, & Gustafsson, 1997; Gijs & Brewaeys, 2007; Murad et al., 2010; Pfäfflin & Junge, 1998). Patients operated on after 1986 did better than those before 1986; this reflects significant improvement in surgical complications (Eldh et al., 1997). Most patients have reported improved psychosocial outcomes, ranging between 87% for MtF patients and 97% for FtM patients (Green & Fleming, 1990). Similar improvements were found in a Swedish study in which “almost all patients were satisfied with sex reassignment at 5 years, and 86% were assessed by clinicians at follow-up as stable or improved in global functioning” (Johansson, Sundbom, Höjerback, & Bodlund, 2010). Weaknesses of these earlier studies are their retrospective design and use of different criteria to evaluate outcomes.

A prospective study conducted in the Netherlands evaluated 325 consecutive adult and adolescent subjects seeking sex reassignment (Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). Patients who underwent sex reassignment therapy (both hormonal and surgical intervention) showed improvements in their mean gender dysphoria scores, measured by the Utrecht Gender Dysphoria Scale. Scores for body dissatisfaction and psychological function also improved in most categories. Fewer than 2% of patients expressed regret after therapy. This is the largest prospective study to affirm the results from retrospective studies that a combination of hormone therapy and surgery improves gender dysphoria and other areas of psychosocial functioning. There is a need for further research on the effects of hormone therapy without surgery, and without the goal of maximum physical feminization or masculinization.

Overall, studies have been reporting a steady improvement in outcomes as the field becomes more advanced. Outcome research has mainly focused on the outcome of sex reassignment surgery. In current practice there is a range of identity, role, and physical adaptations that could use additional follow-up or outcome research (Institute of Medicine, 2011).

APPENDIX E

DEVELOPMENT PROCESS FOR THE STANDARDS OF CARE, VERSION 7

The process of developing *Standards of Care, Version 7* began when an initial SOC “work group” was established in 2006. Members were invited to examine specific sections of SOC, *Version 6*. For each section, they were asked to review the relevant literature, identify where research was lacking and needed, and recommend potential revisions to the SOC as warranted by new evidence. Invited papers were submitted by the following authors: Aaron Devor, Walter Bockting, George Brown, Michael Brownstein, Peggy Cohen-Kettenis, Griet DeCuypere, Petra DeSutter, Jamie Feldman, Lin Fraser, Arlene Istar Lev, Stephen Levine, Walter Meyer, Heino Meyer-Bahlburg, Stan Monstrey, Loren Schechter, Mick van Trotsenburg, Sam Winter, and Ken Zucker. Some of these authors chose to add co-authors to assist them in their task.

Initial drafts of these papers were due June 1, 2007. Most were completed by September 2007, with the rest completed by the end of 2007. These manuscripts were then submitted to the *International Journal of Transgenderism (IJT)*. Each underwent the regular *IJT* peer review process. The final papers were published in Volume 11 (1-4) in 2009, making them available for discussion and debate.

After these articles were published, a *Standards of Care* Revision Committee was established by the WPATH Board of Directors in 2010. The Revision Committee was first charged with debating and discussing the *IJT* background papers through a Google website. A subgroup of the Revision Committee was appointed by the Board of Directors to serve as the Writing Group. This group was charged with preparing the first draft of SOC, *Version 7* and continuing to work on revisions for consideration by the broader Revision Committee. The Board also appointed an International Advisory Group of transsexual, transgender, and gender nonconforming individuals to give input on the revision.

A technical writer was hired to (1) review all of the recommendations for revision – both the original recommendations as outlined in the *IJT* articles and additional recommendations that emanated from the online discussion – and (2) create a survey to solicit further input on these potential revisions. From the survey results, the Writing Group was able to discern where these experts stood in terms of areas of agreement and areas in need of more discussion and debate. The technical writer then (3) created a very rough first draft of SOC, *Version 7* for the Writing Group to consider and build on.

The Writing Group met on March 4 and 5, 2011 in a face-to-face expert consultation meeting. They reviewed all recommended changes and debated and came to consensus on various controversial areas. Decisions were made based on the best available science and expert consensus. These decisions were incorporated into the draft, and additional sections were written by the Writing Group with the assistance of the technical writer.

The draft that emerged from the consultation meeting was then circulated among the Writing Group and finalized with the help of the technical writer. Once this initial draft was finalized it was circulated among the broader SOC Revision Committee and the International Advisory Group. Discussion was opened up on the Google website and a conference call was held to resolve issues. Feedback from these groups was considered by the Writing Group, who then made further revision. Two additional drafts were created and posted on the Google website for consideration by the broader SOC Revision Committee and the International Advisory Group. Upon completion of these three iterations of review and revision, the final document was presented to the WPATH Board of Directors for approval. The Board of Directors approved this version on September 14, 2011.

The plans are to disseminate this version of the SOC and invite feedback for further revisions. The WPATH Board of Directors decides the timing of any revision of the SOC.

Funding

The *Standards of Care* revision process was made possible through a generous grant from the Tawani Foundation and a gift from an anonymous donor. These funds supported the following:

1. Costs of a professional technical writer;
2. Process of soliciting international input on proposed changes from gender identity professionals and the transgender community;
3. Working meeting of the Writing Group;
4. Process of gathering additional feedback and arriving at final expert consensus from the professional and transgender communities, the *Standards of Care, Version 7* Revision Committee, and WPATH Board of Directors;
5. Costs of printing and distributing *Standards of Care, Version 7* and posting a free downloadable copy on the WPATH website;

6. Plenary session to launch the *Standards of Care, Version 7* at the 2011 WPATH Biennial Symposium in Atlanta, Georgia, USA.

Members of the Standards of Care Revision Committee¹

Eli Coleman, PhD (USA)* - Committee chair	Arlene Istar Lev, LCSW (USA)
Richard Adler, PhD (USA)	Gal Mayer, MD (USA)
Walter Bockting, PhD (USA)*	Walter Meyer, MD (USA)*
Marsha Botzer, MA (USA)*	Heino Meyer-Bahlburg, Dr. rer.nat. (USA)
George Brown, MD (USA)	Stan Monstrey, MD, PhD (Belgium)*
Peggy Cohen-Kettenis, PhD (Netherlands)*	Blaine Paxton Hall, MHS-CL, PA-C (USA)
Griet DeCuypere, MD (Belgium)*	Friedmann Pfaefflin, MD, PhD (Germany)
Aaron Devor, PhD (Canada)	Katherine Rachlin, PhD (USA)
Randall Ehrbar, PsyD (USA)	Bean Robinson, PhD (USA)
Randi Ettner, PhD (USA)	Loren Schechter, MD (USA)
Evan Eyler, MD (USA)	Vin Tangpricha, MD, PhD (USA)
Jamie Feldman, MD, PhD (USA)*	Mick van Trotsenburg, MD (Netherlands)
Lin Fraser, EdD (USA)*	Anne Vitale, PhD (USA)
Rob Garofalo, MD, MPH (USA)	Sam Winter, PhD (Hong Kong)
Jamison Green, PhD, MFA (USA)*	Stephen Whittle, OBE (UK)
Dan Karasic, MD (USA)	Kevan Wylie, MB, MD (UK)
Gail Knudson, MD (Canada)*	Ken Zucker, PhD (Canada)

International Advisory Group Selection Committee

Walter Bockting, PhD (USA)	Evan Eyler, MD (USA)
Marsha Botzer, MA (USA)	Jamison Green, PhD, MFA (USA)
Aaron Devor, PhD (Canada)	Blaine Paxton Hall, MHS-CL, PA-C (USA)
Randall Ehrbar, PsyD (USA)	

¹ * Writing Group member

All members of the *Standards of Care, Version 7 Revision Committee* donated their time to work on this revision.

International Advisory Group

Tamara Adrian, LGBT Rights Venezuela (Venezuela)
Craig Andrews, FTM Australia (Australia)
Christine Burns, MBE, Plain Sense Ltd (UK)
Naomi Fontanos, Society for Transsexual Women's Rights in the Phillipines (Phillipines)
Tone Marie Hansen, Harry Benjamin Resource Center (Norway)
Rupert Raj, Shelburne Health Center (Canada)
Masae Torai, FTM Japan (Japan)
Kelley Winters, GID Reform Advocates (USA)

Technical Writer

Anne Marie Weber-Main, PhD (USA)

Editorial Assistance

Heidi Fall (USA)

EXHIBIT I



HEALTH AFFAIRS

THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

JUL 29 2016

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (MANPOWER AND
RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE NAVY (MANPOWER AND
RESERVE AFFAIRS)
ASSISTANT SECRETARY OF THE AIR FORCE (MANPOWER
AND RESERVE AFFAIRS)
DIRECTOR, DEFENSE HEALTH AGENCY
DIRECTOR, HEALTH, SAFETY AND WORK LIFE, U.S. COAST
GUARD

SUBJECT: Guidance for Treatment of Gender Dysphoria for Active and Reserve
Component Service Members

In accordance with Department of Defense Instruction (DoDI) 1300.28, "In-Service Transition for Transgender Service Members," June 30, 2016, and Directive-Type Memorandum (DTM)16-005, "Military Service of Transgender Service Members," June 30, 2016, this memorandum provides guidance for the medical care of transgender Service members. This memorandum supplements requirements in those issuances; it does not supersede any such requirements.

General Provisions:

The Military Health System (MHS) will either provide or arrange consultation for medically necessary care for members on active duty for a period of more than 30 days (referred to as Active Duty Service members (ADSMs) throughout the remainder of this document). Such care is based upon the individual's unique health care needs and, following initial evaluation, may include counseling and behavioral health services, medical support, and assistance with establishing a treatment plan for the Service member's submission to the unit commander, followed by any medically necessary treatment.

Until the DoD is able to promulgate specific clinical practice guidelines for the care of transgender personnel, the MHS will adhere to the attached 2009 version of the Endocrine Society's Standards of Care, "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," as the primary guideline to provide consistent, evidence based care to transitioning patients. Explanation of any clinically indicated deviation from the guideline should be documented in the patient's health record. Clinical Practice Guidelines from other professional societies may also help inform clinical decision making (e.g., the 2015 American Psychological Association Guidelines for Psychological Practice with Transgender and Gender Nonconforming People and the World Professional Association for Transgender Health Standards of Care). Key components of medical care for the purpose of treating gender dysphoria include initial assessment and, based upon that assessment of the individual's needs,

the establishment of a treatment plan which may include real life experience (RLE) that is provided in a manner consistent with the requirements of DoDI 1300.28 and DTM 16-005 regarding RLE, cross-sex hormone therapy, and surgical transition. Treatment plans must be individualized and approved by a military medical provider. The following guidance addresses various stages of treatment:

1. For Active Duty Service members (ADSMs) seeking initial treatment for gender dysphoria, a diagnosis of gender dysphoria must be established by a privileged behavioral health provider (or similarly qualified civilian provider if unavailable in a military facility), with appropriate referral to other types of providers as indicated or required. The assessment should be comprehensive in nature, including exclusion of other causes for dysphoria, and lead to formulation of an initial treatment plan.
2. For ADSMs who have already received a diagnosis of gender dysphoria and established a treatment plan approved by a military medical provider, and who desire to proceed to or continue cross-sex hormone therapy, an endocrinologist or other physician with appropriate professional expertise should exclude medical conditions making hormone therapy unsafe, may initiate or continue hormone therapy if indicated as medically necessary, and monitor response to hormones in accordance with the Endocrine Society's Standards of Care guidelines, to include periodic screening for hormone associated adverse outcomes.
3. ADSMs with an established treatment plan desiring surgical treatment following a period of RLE and who are compliant with all facets of an approved treatment plan should be referred to an appropriately qualified surgeon for evaluation. The surgeon should fully discuss all surgical options and potential complications in order to provide informed consent before surgery is proposed. Consistent with current DoD policies, purely cosmetic or other non-medically necessary surgery is not authorized.
4. Any Service member for whom the Defense Enrollment Eligibility Reporting System has recorded a gender change, or who is in the process of obtaining such a change, must have an ongoing plan to address needed medical care, including follow up of hormone treatment and any appropriate health screening.
5. Unless and until adequate surgical capabilities have been established in DoD Military Treatment Facilities (MTFs), medically necessary surgical treatment will be evaluated using the existing MHS waiver process for private sector care for Active Duty members under the Supplemental Health Care Program (SHCP). This standardized process requires referral through the Service chain of command and review and approval by the Director, Defense Health Agency (DHA).
6. The expectation is for the MHS to provide an interdisciplinary team approach to transition care in accordance with evidence based guidelines and practices, reinforcing at all times the transgender Service member's right to receive all medical care with dignity and respect. Provision of care may involve multiple facilities and require appropriate care coordination between providers. In no circumstance will a provider be required to

deliver care that he or she feels unprepared to provide either by lack of clinical skill or due to ethical, moral or religious beliefs. However, referral to an appropriate provider or level of care is required under such circumstances.

7. As with all other medical conditions, in the first 180 days of service in the military, all personnel must continue to meet the medical standards associated with accession (DoDI 6130.03, "Medical Standards for Appointment, Enlistment, or Induction in the Military Services"). Ongoing fitness for duty and deployment screening after 180 days shall be assessed in accordance with current Service practices and policies applied to other medical conditions.

Central Coordination:

1. Service Central Coordination Cells (SCCC) established under DoDI 1300.28 shall provide multi-disciplinary (e.g., medical, legal, military personnel management) expert advice and assistance to commanders with regard to service by transgender Service members and gender transition in the military to assist commanders in the execution of DoD, Military Department, and Service policies and procedures.
2. The Under Secretary of Defense for Personnel and Readiness (USD(P&R)) has established a Central Coordination Cell with Office of the Secretary of Defense, DHA, and Service representatives to oversee consistent and uniform implementation of DoDI 1300.28, provide consultation to SCCC's, and receive and analyze data reported by the Services. The Central Coordination Cell is not a substitute for SCCC's, but provides information and advice on policy matters, and assistance with identification and coordination of needed treatment resources, when necessary. DHA has provided a senior representative to facilitate coordination of care and services delivered by the managed care support contractors and the DHA Waiver Authority process.
3. To assist Commanders and Service members until each Service establishes its own SCCC, the DoD Central Coordination Cell has established the following website: <https://prext.osd.mil/DoDCCC>. This is a Common Access Card-enabled website for secure questions by all Service members. Policy documents and Frequently Asked Questions reside on this website and questions will be answered by policy, legal and medical experts.

Service and DHA Requirements and Responsibilities:

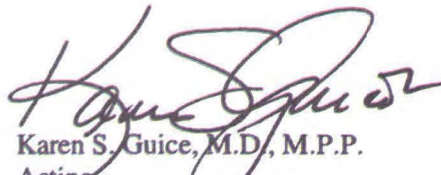
1. Each Service and DHA shall develop and submit an assessment of current Service medical capacity and expertise in providing medical and surgical support for treating gender dysphoria to the USD(P&R) no later than August 31, 2016. This assessment should include a listing of MTFs at which interdisciplinary care and treatment are available or under development for this purpose, and use the attached data reporting template.

2. Each Service and DHA shall develop an education and training plan for both privileged and non-privileged medical personnel no later than November 1, 2016. This plan should detail how the Service will ensure familiarity with applicable Department policies and requirements, evidence-based practice guidelines and standards of care, and any Service-specific policies. To the extent practicable, training plans and requirements, and additional procedural guidance for care and services will be consistent across the MHS, and will be published as DHA procedural guidance.
3. Each Service and DHA shall be prepared to begin supporting transition medical care to transgender ADSMs no later than October 1, 2016. At a minimum, Services will be expected to provide, by referral if necessary, initial assessment, psychological and pharmaceutical support. As directed by the Secretary of Defense, in the period prior to October 1, 2016, the Military Departments and Services will address requests for gender transition from serving transgender Service members on a case-by-case basis, following the spirit and intent of DTM 16-005 and DoDI 1300.28. Until the capability of MHS MTFs to provide surgical transition services has been documented, any proposed genital surgical transition procedures within MTFs shall be prospectively reviewed by the appropriate Surgeon General or, in the case of the National Capital Region facilities, the Director, DHA. Approvals will be reported to the Assistant Secretary of Defense for Health Affairs (ASD(HA)) monthly.
4. The Director, DHA, will ensure that the Managed Care Support Contractors identify appropriate referral resources with providers experienced in care and treatment of transgender persons to ensure availability of care to complement MTF capabilities. An inventory of such resources shall be provided to the ASD(HA) not later than August 31, 2016.
5. The Director, DHA, will evaluate proposed referrals to the TRICARE network for surgical treatment in accordance with the Supplemental Health Care Program (SHCP). MHS care for ADSMs from non-DoD providers is governed by section 1074(c)(2) of title 10, U.S. Code, and section 199.16 of title 32, Code of Federal Regulations. Under these provisions, the SHCP normally follows TRICARE rules, which disallow surgical treatment of gender dysphoria, but the prohibition is subject to waiver for medically necessary care for ADSMs. The Director, DHA, is authorized to grant waivers on a case-by-case basis. Waiver requests will follow existing processes. Each waiver request, with appropriate clinical documentation, should be submitted through the Surgeon General concerned, to the Director, DHA.
6. To the extent a SHCP waiver would be needed to authorize non-surgical care for an ADSM, this memorandum approves such a waiver on a blanket basis if such care is recommended by a military health care provider in accordance with established SHCP procedures and this memorandum.

7. With respect to Reserve Component Service members not on active duty for a period of more than 30 days who initiate or are involved in a gender transition process, the Services shall establish procedures to ensure that a medical diagnosis and treatment plan (or significant revisions to a treatment plan) or a recommendation for a change in a member's gender marker made by a civilian medical provider is reviewed and approved by an appropriate military medical provider and communicated in a timely and efficient manner with the Reserve Component command involved.

ASD(HA) Responsibilities:

1. The ASD(HA) shall establish collaboration with the Veterans Health Administration and academic medical centers to support Service training plans and specialty consultations, including via telemedicine, where necessary and appropriate.
2. The ASD(HA) shall monitor compliance with this memorandum, which may include assessing Service and DHA performance on all provisions contained within this memorandum.



Karen S. Guice, M.D., M.P.P.
Acting

Attachments:
As stated

cc:
Under Secretary of Defense for Personnel and Readiness
Assistant Secretary of Defense (Manpower and Reserve Affairs)
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Joint Staff Surgeon
Medical Office of the Marine Corps

EXHIBIT J

**Department of Health and Human Services
DEPARTMENTAL APPEALS BOARD
Appellate Division**

NCD 140.3, Transsexual Surgery
Docket No. A-13-87
Decision No. 2576
May 30, 2014

DECISION

The Board has determined that the National Coverage Determination (NCD) denying Medicare coverage of all transsexual surgery as a treatment for transsexualism is not valid under the “reasonableness standard” the Board applies. The NCD was based on information compiled in 1981. The record developed before the Board in response to a complaint filed by the aggrieved party (AP), a Medicare beneficiary denied coverage, shows that even assuming the NCD’s exclusion of coverage at the time the NCD was adopted was reasonable, that coverage exclusion is no longer reasonable. This record includes expert medical testimony and studies published in the years after publication of the NCD. The Centers for Medicare & Medicaid Services (CMS), which is responsible for issuing and revising NCDs, did not defend the NCD or the NCD record in this proceeding and did not challenge any of the new evidence submitted to the Board.

Effect of this decision

Since the NCD is no longer valid, its provisions are no longer a valid basis for denying claims for Medicare coverage of transsexual surgery, and local coverage determinations (LCDs) used to adjudicate such claims may not rely on the provisions of the NCD. The decision does not bar CMS or its contractors from denying individual claims for payment for transsexual surgery for other reasons permitted by law. Nor does the decision address treatments for transsexualism other than transsexual surgery. The decision does not require CMS to revise the NCD or issue a new NCD, although CMS, of course, may choose to do so. CMS may not reinstate the invalidated NCD unless it has a different basis than that evaluated by the Board. 42 C.F.R. § 426.563.

CMS must implement this Board decision within 30 days and apply any resulting policy changes to claims or service requests made by Medicare beneficiaries other than the AP for any dates of service after that implementation. With respect to the AP’s claim in

particular, CMS and its contractors must “adjudicate the claim without using the provision(s) of the NCD that the Board found invalid.” 42 C.F.R. § 426.560(b)(1).¹

Legal background

With exceptions not relevant here, section 1862(a)(1)(A) of the Social Security Act (Act) (42 U.S.C. § 1395y(a)(1)(A)) bars Medicare payment for items or services “not reasonable and necessary for the diagnosis or treatment of illness or injury[.]”² CMS refers to this requirement as the “medical necessity provision.” 67 Fed. Reg. 54,534, 54,536 (Aug. 22, 2002). An NCD is “a determination by the Secretary [of Health and Human Services] with respect to whether or not a particular item or service is covered nationally under [title XVIII (Medicare)].” Act §§ 1862(l)(6)(A), 1869(f)(1)(B); *see also* 42 C.F.R. § 400.202 (NCD “means a decision that CMS makes regarding whether to cover a particular service nationally under title XVIII of the Act.”). NCDs “describe the clinical circumstances and settings under which particular [Medicare items and] services are reasonable and necessary (or are not reasonable and necessary).” 67 Fed. Reg. at 54,535. When CMS issues NCDs, they apply nationally and are binding at all levels of administrative review of Medicare claims. 42 C.F.R. § 405.1060. CMS and its contractors use applicable NCDs in determining whether a beneficiary may receive Medicare reimbursement for a particular item or service. 42 C.F.R. §§ 405.920, 405.921.

A Medicare beneficiary “in need of coverage for a service that is denied based on ... an NCD” is an “aggrieved party” who may challenge the NCD by filing a “complaint” with the Board.³ Act § 1869(f)(1); 42 C.F.R. §§ 426.110, 426.320. The complaint must comply with the requirements for a valid complaint in 42 C.F.R. § 426.500 in order to be accepted by the Board. 42 C.F.R. §§ 426.510(b)(2), 426.505(c)(2). After the Board notifies CMS of the receipt of a complaint that is acceptable under the regulations, CMS produces the “NCD record,” which “consists of any document or material that CMS

¹ *See generally* 42 C.F.R. § 426.560(b) (setting out the effects of a Board NCD decision); 42 C.F.R. § 426.555 (specifying what the Board’s decision “may not do”). This decision has no effects beyond those set out in 42 C.F.R. § 426.560(b) and does not impose on CMS or its contractors any orders or requirements prohibited by 42 C.F.R. § 426.555.

² The table of contents to the current version of the Social Security Act, with references to the corresponding United States Code chapter and sections, can be found at http://www.socialsecurity.gov/OP_Home/ssact/ssact-toc.htm.

³ The regulations also provide that a person other than the aggrieved party with an interest in the issues may petition to participate in the review process as an *amicus curiae*. 42 C.F.R. §§ 426.510(f), 426.513. The Board posts on its website notice of the NCD complaint specifying a time period for requests to participate in the review. 42 C.F.R. § 426.510(f).

considered during the development of the NCD” including “medical evidence considered on or before the date the NCD was issued” 42 C.F.R. §§ 426.510(d)(3), 426.515, 426.518(a). The aggrieved party submits a statement “explaining why the NCD record is not complete, or not adequate to support the validity of the NCD under the reasonableness standard,” and CMS may submit a response “in order to defend the NCD.” 42 C.F.R. § 426.525(a), (b). If the Board determines that the NCD record “is complete and adequate to support the validity of the NCD,” the review process ends with the Board’s “[i]ssuance of a decision finding the record complete and adequate to support the validity of the NCD” 42 C.F.R. § 426.525(c)(1), (2). If the Board determines that the record is *not* complete and adequate to support the validity of the NCD, the Board “permits discovery and the taking of evidence . . . and evaluates the NCD” in accordance with the requirements of Part 426, including conducting a hearing, unless the matter can be decided on the written record. 42 C.F.R. §§ 426.525(c)(3), 426.531(a)(2).

Prior to issuing a decision, the Board must review any “new evidence” admitted to the record before the Board and determine whether it “has the potential to significantly affect” the Board’s evaluation. 42 C.F.R. §§ 426.340(a), (b), 426.505(d)(3). “New evidence” is defined as “clinical or scientific evidence that was not previously considered by . . . CMS before the . . . NCD was issued.” 42 C.F.R. § 426.110. If the Board so concludes, the Board stays proceedings for CMS “to examine the new evidence, and to decide whether [to] initiate[] . . . a reconsideration” of the NCD. 42 C.F.R. § 426.340(d). If CMS does not reconsider the NCD, or reconsiders it but does not change the challenged provision, the Board lifts the stay and the NCD challenge process continues. 42 C.F.R. § 426.340(f). At the end of that process, the Board closes the record and issues a decision that the challenged “provision of the NCD is valid” or “is not valid under the reasonableness standard.”⁴ 42 C.F.R. § 426.550. The Board’s decision “constitutes a final agency action and is subject to judicial review” on appeal by an aggrieved party. 42 C.F.R. § 426.566.

⁴ Section 426.547(b) states that the Board must make the decision available at the HHS Medicare Internet site and that “the posted decision does not include any information that identifies any individual, provider of service, or supplier.” CMS has indicated in the preamble to the Part 426 regulations that this provision was meant to protect the privacy of Medicare beneficiaries such as the AP. *See, e.g.*, 68 Fed. Reg. 63,692, 63,708 (Nov. 7, 2003) (“Board decisions regarding NCDs will be made available on the Medicare Internet site, without beneficiary identifying information”).

Case background

The NCD and the NCD record

The challenged NCD, titled “140.3, Transsexual Surgery,” states:⁵

Item/Service Description

Transsexual surgery, also known as sex reassignment surgery or intersex surgery, is the culmination of a series of procedures designed to change the anatomy of transsexuals to conform to their gender identity. Transsexuals are persons with an overwhelming desire to change anatomic sex because of their fixed conviction that they are members of the opposite sex. For the male-to-female, transsexual surgery entails castration, penectomy and vulva-vaginal construction. Surgery for the female-to-male transsexual consists of bilateral mastectomy, hysterectomy and salpingo-oophorectomy, which may be followed by phalloplasty and the insertion of testicular prostheses.

Indications and Limitations of Coverage

Transsexual surgery for sex reassignment of transsexuals is controversial. Because of the lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental. Moreover, there is a high rate of serious complications for these surgical procedures. For these reasons, transsexual surgery is not covered.

NCD Record at 93. CMS’s predecessor, the Health Care Financing Administration (HCFA), published the NCD in the Federal Register on August 21, 1989.⁶ 54 Fed. Reg. 34,555, 34,572 (Aug. 21, 1989); NCD Record at 76, 78, 93, 128. The NCD quotes or paraphrases portions of an 11-page report that the former National Center for Health Care Technology (NCHCT) of the HHS Public Health Service (PHS) issued in 1981, titled

⁵ NCDs are available at http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?list_type=ncd.

⁶ The Federal Register notice stated, “This notice lists those current Medicare national coverage decisions which have been issued in the Medicare Coverage Issues Manual (HCFA Pub. 6).” 54 Fed. Reg. at 34,555.

“Evaluation of Transsexual Surgery” (1981 report).⁷ NCD Record at 13-23. The NCHCT forwarded the 1981 report to HCFA with a May 6, 1981 memorandum stating that the 1981 report “concludes that transsexual surgery should be considered experimental because of the lack of proven safety and efficacy of the procedures for the treatment of transsexualism” and recommending “that transsexual surgery not be covered by Medicare at this time.” *Id.* at 12.

The NCD record includes three April 1982 letters from the American Civil Liberties Union (ACLU) of Southern California disagreeing with HCFA’s noncoverage determination. *Id.* at 24-25, 26, 41-42. The ACLU submitted letters and affidavits from physicians and therapists supporting the medical necessity of transsexual surgery and taking issue with the non-coverage determination. *Id.* at 27-75. On May 11, 1982, the HCFA physicians panel, by a vote of five to two, recommended against referring the ACLU’s submissions to PHS, “on the basis that it does not contain information about new clinical studies or other medical and scientific evidence sufficiently substantive to justify reopening the previous PHS assessment.” *Id.* at 7, 9. Thus, although the NCD was issued in 1989, it was based on the analysis of medical and scientific publications in the 1981 report.

The NCD complaint

The AP in this case, a Medicare beneficiary whose insurer denied a physician’s order for sex reassignment surgery (transsexual surgery), filed an acceptable NCD complaint and supporting materials. CMS submitted the NCD record on May 15, 2013, and the AP submitted a statement of why the NCD record is not complete or adequate to support the validity of the NCD under the reasonableness standard (AP Statement) on June 14, 2013. The Board granted unopposed requests by six advocacy organizations to participate as amici curiae in the NCD review by filing written briefs arguing that the NCD was invalid. (Four of the amici submitted a joint brief.)⁸

⁷ The concluding summary of the 1981 NCHTC report stated in relevant part:

Transsexual surgery for sex reassignment of transsexuals is controversial. There is a lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism. There is evidence of a high rate of serious complications of these surgical procedures. The safety and effectiveness of transsexual surgery as a treatment of transsexualism is not proven and is questioned. Therefore, transsexual surgery must be considered still experimental.

NCD Record at 19.

⁸ The six amici are the Human Rights Campaign (HRC) and the World Professional Association for Transgender Health (WPATH), which each submitted briefs, and the FORGE Transgender Aging Network, the National Center for Transgender Equality, the Sylvia Rivera Law Project, and the Transgender Law Center, which submitted a joint brief.

On June 26, 2013, CMS notified the Board that it “declines to submit a response” to the AP’s statement. On December 2, 2013, the Board ruled that the NCD record “is not complete and adequate to support the validity of the NCD[.]” *NCD 140.3, Transsexual Surgery*, NCD Ruling No. 2 (Dec. 2, 2013) (NCD Ruling).⁹ The parties then jointly reported that they did not intend to submit additional evidence (except for curricula vitae (CVs) of the AP’s witnesses) or cross-examine any witness and asked the Board to close the NCD review record to the taking of evidence and decide the case based on the written record.

The Board determined that the new evidence in the record had the potential to significantly affect its review of the NCD and, as required, stayed proceedings for 10 days for CMS to examine the new evidence and decide whether to reconsider the NCD.¹⁰ *Order Closing Record & Staying Proceedings for CMS to Determine Whether to Reconsider NCD* (Feb. 25, 2014) (Order); 42 C.F.R. §§ 426.340(d), 426.505(d)(3). Two days later, CMS informed the Board by email that it “does not wish to reconsider the NCD.” On February 28, 2014, the Board lifted the stay and informed the parties that it would proceed to decision.

The record developed before the Board

The record before the Board consists of the NCD record, the briefs submitted by the AP and the amici and evidence submitted by the AP and one of the amici, the Human Rights Campaign. Since neither party submitted argument or evidence (except for the CVs) after the Board’s Ruling, the Board treats the AP statement as the AP’s brief in this appeal.¹¹ The AP submitted written declarations made under penalty of perjury from a clinical psychologist and a physician, and two notarized physician letters submitted to an Administrative Law Judge in the Department of Health and Human Services Office of Medicare Hearings and Appeals in another matter. The AP described the witnesses, who are active in the field of treating transgender persons, as experts and submitted their resumes or CVs. AP Statement at 9; AP complaint; AP/CMS e-mail (Jan. 7, 2014).

⁹ The NCD Ruling is at <http://www.hhs.gov/dab/decisions/dabdecisions/ncd1403.pdf>.

¹⁰ The Board also published on its website notice providing an additional time period for interested parties to submit participation requests; none were received.

¹¹ Most of the AP’s evidence other than witness statements is an appendix of sources the clinical psychologist cited in her declaration. We refer to these materials as the AP’s exhibits (AP Exs.) and cite to the page numbers used in the publications in which they appeared. In addition, the physician’s declaration includes an appendix of 20 unnumbered pages of insurance regulations from four states and the District of Columbia barring exclusion of sex reassignment surgery as medically necessary treatment for severe gender dysphoria. One of the amici, the Human Rights Campaign, submitted 62 exhibits with its brief (“HRC Exs.”).

CMS did not challenge the witnesses' qualifications as experts or seek to cross-examine them. We summarize their qualifications when we address their testimony below. In this decision we use the term "new evidence" to refer to the evidence submitted to us by the AP and amici to distinguish it from the evidence used to support the NCD which, as noted, consists principally of the 1981 report. Under the regulatory definition in 42 C.F.R. § 426.110, "new evidence" would also include any evidence submitted by CMS in response to an NCD complaint that was not considered by CMS before the NCD was issued. In this case, however, as we discuss below, CMS submitted no "new evidence."

Standard of review

The Board "evaluate[s] the reasonableness" of an NCD by determining whether it "is valid [or] is not valid under the reasonableness standard," which requires us to uphold the NCD "if the findings of fact, interpretations of law, and applications of fact to law by ... CMS are reasonable" based on the NCD record and the relevant record developed before us. Act § 1869(f)(1)(A)(iii); 42 C.F.R. §§ 426.110, 426.531(a), 426.550(a). The Board "defer[s] only to the reasonable findings of fact, reasonable interpretations of law, and reasonable applications of fact to law by the Secretary." Act § 1869(f)(1)(A)(iii); 42 C.F.R. § 426.505(b).

During the review, the aggrieved party bears the burden of proof and the burden of persuasion for the issues raised in an NCD complaint; the burden of persuasion is judged by a preponderance of the evidence. 42 C.F.R. § 426.330. CMS has explained that "[s]o long as the outcome [in the NCD] is one that could be reached by a rational person, based on the evidence in the record as a whole (including logical inferences drawn from that evidence), the determination must be upheld," and that if CMS "has a logical reason as to why some evidence is given more weight than other evidence," the Board "may not overturn the determination simply because they would have accorded more weight to the evidence in support of coverage." 68 Fed. Reg. at 63,703.

Analysis

The NCD is invalid because a preponderance of the evidence in the record as a whole supports a conclusion that the NCD's stated bases for its blanket denial of coverage for transsexual surgery are not reasonable.

As previously stated, the NCD was based principally on the 1981 report findings that the safety and effectiveness of transsexual surgery had not been proven. The AP argues that these findings are not "supportable by the current state of medical science" and "not reasonable in light of the current state of scientific and clinical evidence and current medical standards of care" and are contradicted by studies conducted in the 32 years since the 1981 report. AP Statement at 6-7, 14. The amici made similar arguments. *See, e.g.,* WPATH Br. at 13 ("since [the NCD] was issued, it has been repeatedly

demonstrated that SRS [sex reassignment surgery] is safe, effective, and indisputably necessary treatment for certain individuals with severe GID [gender identity disorder]”). As we discuss below, the new evidence, which is unchallenged, indicates that the bases stated in the NCD and the NCD record for denying coverage, even assuming they were reasonable when the NCD was issued, are no longer reasonable.

A. The fact that the new evidence is unchallenged and the NCD record undefended is significant.

As we stated earlier, the AP has the burden of proof by a preponderance of the evidence that an NCD is invalid under a reasonableness standard. In deciding whether the AP has met this burden, we must weigh the evidence in the record before us. Thus, we consider it important to note at the outset that the only evidence before us, other than the record for the NCD, which consists principally of the 1981 report, is the new evidence submitted by the AP and the amicus HRC. CMS submitted the NCD record, as it was required to do, but has not argued that that record or any other evidence supports the NCD. CMS also did not elect to cross-examine the AP’s witnesses, has not challenged their testimony or professional qualifications and joined the AP in asking the Board to decide the appeal based on the written record. *See* AP/CMS e-mail (Jan. 7, 2014). The preamble to the regulations that implement the NCD statute states that the “reasonableness standard . . . recognizes the expertise of . . . CMS in the Medicare program—specifically, in the area of coverage requiring the exercise of clinical or scientific judgment.” 68 Fed. Reg. at 63,703 (emphasis added). Accordingly, in determining whether the NCD is valid under the reasonableness standard, we must accord some deference to CMS’s position, and its decision not to defend the NCD or challenge the new evidence in this case has some significance for our decision-making.

Apart from the absence of any challenge to the new evidence or defense of the NCD record, we find the new evidence credible and persuasive on its face.¹² We have no difficulty concluding that the new evidence, which includes medical studies published in the more than 32 years since issuance of the 1981 report underlying the NCD, outweighs the NCD record and demonstrates that transsexual surgery is safe and effective and not experimental. Thus, as we discuss below, the grounds for the NCD’s exclusion of coverage are not reasonable, and the NCD is invalid.

¹² For this reason, we found it unnecessary to exercise our independent authority to “consult with appropriate scientific or clinical experts concerning clinical and scientific evidence.” *See* 42 C.F.R. § 426.531(b).

B. The new evidence indicates acceptance of criteria for diagnosing transsexualism.

Transsexual surgery is a treatment option for the medical condition of transsexualism. The NCD recognized that transsexualism is a diagnosed medical condition. The 1981 report stated that transsexualism “is defined as an overwhelming desire to change anatomic sex stemming from the fixed conviction that one is a member of the opposite sex.” NCD Record at 13, citing Dorland’s Illustrated Medical Dictionary, 25th ed. The 1981 report recognized that the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders issued in 1980 (DSM III) had “included for the first time the diagnostic category of ‘Transsexualism.’” NCD Record at 13. Nonetheless, the 1981 report expressed concern that diagnosing transsexualism was “problematic” because, the report contended, the criteria for establishing the diagnosis “vary from center to center and have changed over time.” NCD Record at 14.

One of the AP’s expert witnesses, Randi Ettner, Ph.D., a clinical psychologist, testified that the expressed basis for this concern is “completely untrue now.” Ettner Supp. Decl. at ¶ 5. Dr. Ettner stated that “Gender Identity Disorder is a serious medical condition codified in the International Classification of Diseases (10th revision; World Health Organization) and the [DSM].”¹³ Ettner Decl. at ¶ 10; *see also* Ettner Supp. Decl. at ¶ 6 (similar testimony). She described the condition as follows:

The disorder is characterized by intense and persistent discomfort with one’s primary and secondary sex characteristics—one’s birth sex. The suffering that arises is often described as “being trapped in the wrong body.” The psychiatric term for this severe and unremitting emotional pain is “gender dysphoria.”

Ettner Decl. at ¶ 10. Dr. Ettner’s declaration and CV state that she has a doctorate in psychology, has evaluated or treated between 2,500 and 3,000 individuals with GID and mental health issues related to gender variance, has published three books, including *Principles of Transgender Medicine and Surgery*, has authored articles in peer-reviewed journals, and is a member of the board of directors of the World Professional Association for Transgender Health (WPATH) and an author of the WPATH Standards of Care for

¹³ The record indicates that the term “transsexualism” that was used in the NCD and the DSM-III was succeeded in the DSM-IV and DSM-V by the terms “Gender Identity Disorder” (GID) and “gender dysphoria.” AP Statement at 1 n.1; Ettner Supp. Decl. at ¶ 6; Hsiao Decl. at ¶ 11; AP Ex. 7, at 208; WPATH Br. at 2 n.3. In this decision, we use the term “transsexualism” because it is used in the NCD, but our decision should be read as encompassing the successor terminology as well.

the Health of Transsexual, Transgender, and Gender-Nonconforming People. *Id.* at ¶¶ 3-6; see also *Sundstrom v. Frank*, 630 F. Supp. 2d 974, 986-87 (E.D.Wis. 2007) (“Dr. Ettner’s experience speaks for itself ... the doctor has conducted research and has been an instructor specializing in the etiology, diagnosis and treatment of GID [and] is the editor of a medical textbook in which she wrote the chapter of that book on the etiology of GID. The court finds that Dr. Ettner is sufficiently qualified to provide expert testimony.”).

We find nothing in the new evidence that would undercut Dr. Ettner’s statement. The DSM-IV-TR (text revision), published in 2000, continues to recognize “transsexualism” as a diagnosed medical condition, although it refers to the same disorder as GID and identifies criteria for diagnosing GID in adolescents and adults that are consistent with Dr. Ettner’s description, albeit more detailed. The criteria include “strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex)” that is “manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex;” “[p]ersistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex” that is “manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex;” and “[t]he disturbance is not concurrent with a physical intersex condition.” AP Ex. 4, at 581. The DSM-IV-TR states that if GID is present in adults, “[t]he disturbance can be so pervasive that the mental lives of some individuals revolve only around those activities that lessen gender distress.” *Id.* at 576, 78. The WPATH brief indicates that transsexualism or GID remains a diagnostic category in the fifth edition of the DSM issued in 2013 (DSM-V), which uses the term “Gender Dysphoria.” WPATH Br. at 2, n.3.

The DSM has been recognized as a primary diagnostic tool of American psychiatry. See *O’Donnabhain v. Comm’r of Internal Revenue*, 134 T.C. 34, at 60 (2010) (stating “all three experts agree [that the DSM-IV-TR] is the primary diagnostic tool of American psychiatry”); see also AP Ex. 3, at 1¹⁴ (resolution of American Medical Association House of Delegates noting the DSM description of GID as “a persistent discomfort with one’s assigned sex and with one’s primary and secondary sex characteristics, which causes intense emotional pain and suffering” that “if left untreated, can result in clinically significant psychological distress, dysfunction, debilitating depression and, for some people without access to appropriate medical care and treatment, suicidality and death”).

¹⁴ American Medical Association House of Delegates, *Resolution 122 (A-08), Removing Financial Barriers to Care for Transgender Patients* (2008).

We conclude that to the extent the NCD was based on concerns expressed in the NCD record about problems diagnosing transsexualism, that concern is unreasonable based on the new evidence.

C. The new evidence indicates that transsexual surgery is safe.¹⁵

The 1981 report stated that transsexual surgery “cannot be considered safe because of the high complication rates.” NCD Record at 18. The 1981 report identified surgical complications including “rectovaginal fistulas, perineal abscesses, introital and deep vaginal stenosis, and vaginal shortening” in male-to-female (MF) patients, and “rejection of the testicular implants, scrotal fusion, and phalloplasty infections” in female-to-male (FM) patients, and states that “[m]ultiple complications for individual patients and secondary surgeries to correct complications or to improve on undesirable results are not uncommon.” *Id.* at 15 (citations omitted). The AP argues that “advancements in surgical techniques have dramatically reduced the risk of complications from sex reassignment surgery and the rates of serious complications from such surgeries are low” and that the studies cited in the 1981 report “evaluated outdated surgical techniques that have been replaced with improved, safer procedures.” AP Statement at 7, 10. The new evidence supports the AP.

Expert witness Katherine Hsiao, M.D., testified that hysterectomies and mastectomies are common procedures used to treat gender GID in transgender men (FM) and “are routinely performed in other contexts, such as in cases of breast cancer, ovarian cancer, uterine cancer and/or cervical cancer” Hsiao Decl. at ¶ 11. These procedures, she stated, “have low rates of complications” and are “generally identical whether performed on transgender men to treat gender dysphoria or to treat women for these other conditions.”¹⁶ *Id.* Dr. Hsiao also stated that “insurance companies routinely cover the costs associated” with hysterectomies. *Id.* Dr. Hsiao testified that based on her own practice of providing surgery to transgender men, “gender affirming surgeries for transgender men are extremely safe and have very low rates of serious complications,”

¹⁵ We are unable to discuss in the space of this decision all of the new evidence and see no need to do so since it is all unchallenged. However, we find nothing in the new evidence not discussed that would alter our conclusion that the NCD is invalid, at least absent argument or counter-evidence from CMS. We have attached to this decision an Overview of the Scientific Literature in the New Evidence.

¹⁶ Dr. Hsiao testified without contradiction that a “serious complication” of surgery—

is generally understood among surgeons to include death, conditions requiring an unplanned admission to the Intensive Care Unit or unplanned readmission to the hospital within 30 days, severe hemorrhage requiring transfusion of several units of blood product, permanent disability, an intraoperative injury requiring an unplanned intervention during the surgical procedure, permanent brain damage, or cardiac arrest.

Hsiao Decl. at ¶ 9.

that she has performed hysterectomies for transgender men for the past ten years and that those procedures “are generally identical to the ones I perform on women to treat early cancer or other conditions.” *Id.* at ¶ 20. Dr. Hsiao reports having “typically performed multiple obstetrical, gynecologic, or other pelvic surgeries every week, including but not limited to hysterectomies and other advanced pelvic surgeries targeting the reproductive system and adjacent organs” *Id.* at ¶ 6. Dr. Hsiao’s declaration and CV indicate that she is certified by the American Board of Obstetrics and Gynecology, is the chief of the division of gynecology and the director of Ob/Gyn resident education at a California medical center and an assistant clinical professor in the department of obstetrics, gynecology and reproductive medicine at the University of California at San Francisco. *Id.* at ¶¶ 3-6; CV.

Dr. Hsiao further stated, regarding MF transsexual surgery, that she has been part of a surgical team that performed surgery to create a neovagina in women born with a congenital “complete or partial absence of a vagina, cervix, and uterus,” a condition called Mayer-Rokitansky-Kuster-Hauser syndrome, or MRKH. Hsiao Decl. at ¶ 12. She stated that this procedure has “a low rate of complications,” and that the associated surgical costs are, in her experience, “routinely cover[ed]” by insurance companies for women born with MRKH. She stated that while women with MRKH “can never have biological children . . . the role of surgery is essential to affirm their gender identity and to align their anatomy with that identity.” *Id.*

Dr. Ettner stated that “[t]here is no scientific or medical basis” for the NCD’s statement that sex reassignment surgery has not been proven safe and has a high rate of serious complications; that the “[r]ates of complications during and after sex reassignment surgery are relatively low, and most complications are minor;” and that the risk of complications “has, moreover, been dramatically reduced since 1985.” Ettner Decl. at ¶¶ 32, 34. Dr. Ettner testified that during eight years at the Chicago Gender Clinic she “regularly consulted with our surgeon” and is “aware of only two major surgical complications, both of which were immediately repaired.” *Id.* at ¶ 36. She stated that the clinic “as a whole has a 12 percent complication rate for genital surgery” and that “the vast majority of those complications [were] minor, all were easily corrected, and none involved surgical site infection or readmission.” *Id.* Dr. Ettner stated the 1981 report’s discussion of surgical complication rates was “outdated and irrelevant based on current medical practices and procedures.” Ettner Supp. Decl. at ¶ 9. In particular, she stated that one of the studies cited in the 1981 report’s discussion of complications (Laub & Fisk 1974) reflected the use of a MF surgical technique that “led to unacceptably high rates of fistulae and other complications” and was later abandoned by the study’s authors. *Id.* at ¶ 10.

Another of the AP’s expert witnesses, Marci L. Bowers, M.D., stated in her notarized letter that in her experience of performing gender-related surgeries, transsexual surgery “does not have a higher rate of complication than any other surgery, and in fact has very

few complications, which are mainly minor in nature.” Bowers Letter at 1 (Mar. 5, 2013), Att. to AP Statement. Dr. Bowers stated that she performs approximately 220 gender-related surgeries annually and has performed over 1000 “Male to Female Gender Corrective Surgeries.” *Id.* Her CV indicates that she has served as the Chair of the Department of Obstetrics and Gynecology at the Swedish (Providence) Medical Center in Seattle.

The fourth expert witness, Sherman N. Leis, M.D., stated that he personally “perform[s] several gender reassignment procedures each week” and has “seen only relatively minor complications which are easily treated” and has “thus far seen no life threatening complications from any of the transgender surgeries” he has performed. Leis Letter at 2 (Feb. 28, 2013), Att. to AP Statement. Dr. Leis’s letter and CV indicate that he is Board-certified in plastic and reconstructive surgery and in general surgery. *Id.* at 1.

The testimony of Drs. Ettner and Hsiao is based on studies as well as personal experience. Dr. Hsiao testified that she reviewed five studies in the AP exhibits “that include complication rate data and information for gender affirming surgeries performed in recent years” and that “[n]one of these five studies reported high rates of serious complications.” Hsiao Decl. at ¶¶ 13-14, citing studies at AP Exs. 2, 9, 14, 21, 28. She stated that “almost all of the complications listed in these studies, such as urinary incontinence or retention, stenosis or stricture, bleeding, recto-vaginal fistula, and partial necrosis, are not specific to sex reassignment surgeries, but rather are known potential side effects of any type of urogenital surgery which are covered by Medicare.” *Id.* at ¶ 15. She further testified that “every complication tracked in [Jarolim, et al. (2009)] for instance, falls into this category and none of them are serious;” that “[t]he Spehr (2007) study includes similar types of complications at very low rates;” and that “none of the complications listed in Lawrence (2006) are serious and many of them are consistent with what would be potential, expected outcomes for any urogenital surgery.” *Id.* at 15-17, citing studies at AP Exs. 14,¹⁷ 21,¹⁸ 28.¹⁹ She also stated that of the four “potentially serious” complications noted in the Amend (2013) study of 24 MF patients, none “were serious as that term is generally understood.” *Id.* at ¶ 14, citing study at AP Ex. 2.²⁰

¹⁷ Ladislav Jarolim, et al., *Gender Reassignment Surgery in Male-to-Female Transsexualism: A Retrospective 3-Month Follow-up Study with Anatomical Remarks*, 6 J. Sex. Med. 1635-44 (2009).

¹⁸ Anne A. Lawrence, *Patient-Reported Complications and Functional Outcomes of Male-to-Female Sex Reassignment Surgery*, 35 Arch. Sex. Behav. 717-27 (2006).

¹⁹ Christiane Spehr, *Male-to-Female Sex Reassignment Surgery in Transsexuals*, 10 Int’l J. Transgenderism 25-37 (2007).

²⁰ Bastian Amend, et al., *Surgical Reconstruction for Male-to-Female Sex Reassignment*, 64 Eur. Urol. 1-9 (2013).

Dr. Hsiao further stated that Eldh et al. (1997) compared complication rates for surgeries performed before and after 1986 and showed that “[n]early all of the surgical complication rates decreased significantly over time.” Hsiao Decl. at ¶ 18, citing study at AP Ex. 9.²¹ Dr. Hsiao stated that “fistulas, in particular, which are a risk of many urogenital surgeries, decreased from 18 percent in surgeries before 1986 to only 1 percent between 1986 and 1995,” and that “the only fistula that occurred after 1985 ‘closed spontaneously,’ meaning without the need for any medical intervention.” *Id.* Eldh, Dr. Hsiao stated, showed that “[t]here is not a high rate of serious complications in any of the surgeries performed after 1986” and she noted that “there have been nearly 20 years of additional surgical progress since the last surgery tracked.” *Id.*

Dr. Ettner cited the same five studies as showing that surgical outcomes were “far superior” after 1985 due to “improvements in technique, shortened hospital stays and improvements in postoperative care,” that significant surgical complications were uncommon; that only a low percentage of patients experienced complications, which were successfully resolved; and that “the complication rate is low and most complications can be overcome by adequate correctional interventions.” Ettner Decl. at ¶¶ 34-35.

We find no reason to discount the opinions of these experts or their representations regarding the findings in the studies they cite. We have conducted our own review of the studies cited by Dr. Hsiao and Dr. Ettner and find them consistent with these opinions and representations. We note, for example, that Eldh, which divided the study group into those operated on before 1986 and those operated on from 1986–1995, made findings tending to support these expert opinions. The Eldh study states:

After 1985 the outcome of surgery became much better not only because of changes in management but also because of improvements in surgical technique, preoperative planning, and postoperative treatment. Total time spent in hospital decreased dramatically after 1985 because the number of procedures was less and the rate of early and late postoperative complications dropped. Haemorrhage and haematoma were common in both groups, predominantly originating from the spongy tissue of the urethra. Infections occurred less often in the late group perhaps as a result of preoperative antibiotic prophylaxis. Serious complications like fistula formation and partial flap necrosis were rare after 1985, though they were common before then. The reason for the lower fistula rate in the later group may be ascribed to better anatomical knowledge of this region and a more precise surgical technique. There was only one rectovaginal fistula after 1985 and this fistula closed spontaneously.

²¹ Jan Eldh, et al., *Long-Term Follow Up After Sex Reassignment Surgery*, 31 Scand. J. Plast. Reconstr. Surg. Hand Surg. 39-45 (1997).

AP Ex. 9, at 44. Dr. Hsiao stated that those findings are “consistent with what I would expect to find when comparing surgeries, and surgical techniques, over a long period of time.” Hsiao Decl. at ¶ 18; *see also* WPATH Br. at 9-10 (citing Eldh and stating that “while early sex reassignment surgeries were sometimes accompanied by serious complications like fistulas or necrotic tissue, the rate of such complications has dropped dramatically with the advent of more sophisticated surgical techniques, among other reasons”).

We conclude that the AP has shown that the NCD’s statement that transsexual surgery is unsafe and has a high rate of complications is not reasonable in light of the evolution of surgical techniques and the studies of outcomes discussed in the unchallenged new evidence presented here.

D. The new evidence indicates that transsexual surgery is an effective treatment option in appropriate cases.²²

1. The expert testimony and studies on which the experts rely support the surgery’s effectiveness.

The AP argues that studies conducted after the 1981 report was issued confirm that transsexual surgery is an effective treatment for persons with severe gender dysphoria, and the expert testimony and studies support that argument. AP Statement at 7-8.

Dr. Ettner testified that “[b]ased on decades of extensive scientific and clinical research, the medical community has reached the consensus that altering a transsexual individual’s primary and secondary sex characteristics is a safe and effective treatment for persons with severe Gender Identity Disorder.” Ettner Decl. at ¶ 13.²³ With regard to effectiveness in particular, Dr. Ettner testified that “more than three decades of research confirms that sex reassignment surgery is therapeutic and therefore an effective treatment for Gender Identity Disorder” and that “for many patients with severe Gender Identity

²² We use the term “appropriate cases” because we do not read the new evidence as necessarily stating that transsexual surgery is appropriate in all cases of transsexualism, and our conclusion that the NCD’s blanket preclusion of Medicare coverage for transsexual surgery is invalid does not require a finding to that effect. However, it is worth noting that WPATH has developed, in its standards of care, criteria for the use of different transsexual surgical procedures. *See, e.g.*, WPATH “[c]riteria for hysterectomy and salpingo-oophorectomy in [FM] patients and for orchiectomy in [MF] patients.” AP Ex. 7, at 202 (E. Coleman, et al., *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, Version 7, 13 Int’l J. Transgenderism 165–232 (2011)).

²³ Dr. Ettner in her declaration focuses on genital surgery for the male-to-female (MF) transsexual. *See* Ettner Decl. at ¶ 8. Dr. Hsiao’s testimony addressed procedures performed on FM patients. Hsiao Decl. at ¶¶ 7, 11, 20-21.

Disorder, sex reassignment surgery is the only effective treatment.” *Id.* at ¶ 19. She concluded that “[t]he NCD’s determination regarding efficacy is not reasonably supported by scientific or clinical evidence, or standards of professional practice, and fails to take into account the robust body of research establishing that surgery relieves, and very often completely eliminates, gender dysphoria.” *Id.* at ¶ 31.

Dr. Bowers stated that “[m]any patients report a dramatic improvement in mental health following surgery, and patients have been able to become productive members of society, no longer disabled with severe depression and gender dysphoria.” Bowers Letter at 1. She concluded that “Gender Corrective Surgery has been shown to be a life-saving procedure, and is unequivocally medically necessary.” *Id.* Dr. Leis stated that “[m]edical literature reports a dramatic drop in the incidence of depression and suicide attempt[s] by individuals who have undergone gender reassignment, indicating that many lives have been saved because of this surgery,” that “there is a very low incidence of ‘regret’” of “only about 1% of patients who have had gender reassignment surgery” and that “I personally have never had a single patient who has regretted having this surgery.” Leis Letter at 2.

Dr. Ettner cited 20 studies published between 1987 and 2010 as showing the effectiveness of transsexual surgery. Ettner Decl. at ¶¶ 20-26, 28-30. She emphasized three studies, two of which were published in 1998 and 2007 and analyze other studies of the treatment of transsexuals published during the years 1961 to 1991 and 1990 to 2007, respectively. *Id.* at ¶¶ 20-22, citing studies at AP Exs. 10, 25, 27; *see also* WPATH Br. at 7-8 (discussing the same three studies). The 1998 study (Pfafflin & Junge) reviewed “30 years of international follow-up studies of approximately two thousand persons who had undergone sex reassignment surgery” including more than 70 individual studies and eight published reviews from four continents. AP Ex. 25 at unnumbered page 1.²⁴ As “general results,” the researchers in the 1998 study stated that the studies they reviewed concluded “that gender reassigning treatments are effective,” that positive, desired results outweigh the negative or non-desired effects, and that “[p]robably the most important change that is found in most research is the increase of subjective satisfaction [which] contrasts markedly to the subjectively unsatisfactory start position of the patients.” *Id.* at 45, 49. The study’s summary, which it qualified as a “simplification,” stated that the studies reviewed show that “[i]n over 80 qualitatively different case studies and reviews from 12 countries, it has been demonstrated during the last 30 years that the treatment that includes the whole process of gender reassignment is effective.” *Id.* at 66. The summary stated that all “follow-up studies mostly found the desired effects” the most important of

²⁴ Friedemann Pfafflin & Astrid Junge, *Sex Reassignment: Thirty Years of International Follow-Up Studies After Sex Reassignment Surgery: A Comprehensive Review 1961-1991* (Roberta B. Jacobson & Alf B. Meier trans., 1998) (1992) (<http://web.archive.org/web/20061218132346/http://www.symposium.com/ijt/pfaefflin/1000.htm>, accessed May 29, 2014).

which the patients felt were “the lessening of suffering” and “desired changes in the areas of partnership and sexual experience, mental stability and socio-economic functioning level.” *Id.* at 66-67.

The 2007 study, Gijs & Brewaeys, which examined the results of 18 studies published between 1990 and 2006, states that sex reassignment “is the most appropriate treatment to alleviate the suffering of extremely gender dysphoric individuals” and that “96% of the persons who underwent [surgery] were satisfied and regret was rare.” AP Ex. 10, at 215, cited in Ettner Decl. at ¶ 22, WPATH Br. at 7.²⁵ Two of the reviewed studies showed that “[s]uicidality was significantly reduced postoperatively” and that in MF patients there were no suicide attempts after surgery as opposed to three attempts before surgery. AP Ex. 10, at 188, 192.

Dr. Ettner and WPATH also cited what Dr. Ettner described as “a large-scale prospective study” finding “that after surgery there was ‘a virtual absence of gender dysphoria’ in the cohort and that the ‘results substantiate previous conclusions that sex reassignment is effective.’” Ettner Decl. at ¶ 21, citing Smith et al. (2005), AP Ex. 27;²⁶ WPATH Br. at 8. Dr. Ettner concluded that Smith et al. and other studies have, variously, “shown that by alleviating the suffering and dysfunction caused by severe gender dysphoria, sex reassignment surgery improves virtually every facet of a patient’s life,” including “satisfaction with interpersonal relationships and improved social functioning,” “improvement in self-image and satisfaction with body and physical appearance,” and “greater acceptance and integration into the family[.]” Ettner Decl. at ¶ 24, citing studies at AP Exs. 1, 12, 15, 19, 22, 26, 27, 30. She also cited nine studies as having “shown that surgery improves patients’ abilities to initiate and maintain intimate relationships.” *Id.* at ¶ 25, citing studies at AP Exs. 8, 13, 14, 16, 20-22, 26, 27.

Based on our own review of the cited studies, we find no reason to question the expert testimony about them. In general, the studies included interviewing post-operative patients with a variety of surveys or questionnaires to assess changes in different aspects of their lives and psychological symptoms following surgery. The studies also generally used statistical techniques to assess the results. The studies were conducted in countries including the United States, Canada, Sweden, the Czech Republic, Israel, Brazil, The Netherlands, and Belgium.

²⁵ Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007).

²⁶ Yolanda L.S. Smith et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals*, 35 Psychol. Med. 89-99 (2005).

We note that these studies are scientific writings and do not make sweeping pronouncements or claim discoveries beyond possible doubt. Indeed, the authors sometimes qualify the results and caution against drawing overly broad and simplistic conclusions. *See, e.g.*, AP Ex. 25, at 66 (Pfafflin & Junge, qualifying the study's summary of its conclusion as a simplification). This, in our view, enhances their facial credibility. Nonetheless, even keeping in mind the possible limitations of these studies, they support the AP's position that transsexual surgery has gained broad acceptance in the medical community.

2. *The 1981 report's expressed concern about an alleged lack of controlled, long-term studies is not reasonable in light of the new evidence.*

The 1981 report summarized the findings of nine studies on “[t]he result or outcome of” transsexual surgery. NCD record at 15-18. With respect to those studies, the report stated that “surgical complications are frequent, and a very small number of post-surgical suicides and psychotic breakdowns are reported.” *Id.* at 17-18. However, the report also acknowledged that eight of those nine studies “report that most transsexuals show improved adjustment on a variety of criteria after sex reassignment surgery, and that “[i]n all of these studies the large majority of those who received surgery report that they are personally satisfied with the change[.]” NCD Record at 17. Notwithstanding its discussion of these studies, the 1981 report (and the NCD) cited an alleged “lack of well controlled, long term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism” as a ground for finding the procedures “experimental.” *Id.* at 19. The 1981 report did not define “long term” for the purpose of assigning weight to study results and the NCD record provided no clarification of that phrase. The 1981 report noted “post-operative followup” and “followup” times for eight of the nine studies on the outcomes of surgery, with “average,” “mean” or “median” periods ranging from 25 months to over eight years, and individual periods from three months to 13 years. NCD Record at 15-17. If these studies do not qualify as acceptable long-term studies, the basis for such a conclusion is not adequately explained in the NCD record.

Even assuming the studies cited in the 1981 report could be viewed as not sufficiently “long-term,” Dr. Ettner stated that “there are numerous long-term follow-up studies on surgical treatment demonstrating that surgeries are effective and have low complication rates” and, as discussed above, her testimony cited some of those studies. Ettner Decl. at ¶ 26. CMS does not challenge this statement, and we find no reason to question it. We note that the participants in one study Dr. Ettner cited had a mean interval since

vaginoplasty of 75.46 months. AP Ex. 30, at 754.²⁷ We also note that the 18 studies published between 1990 and 2006 and encompassing 807 MF and FM patients analyzed in Gijs & Brewaeys (2007) had mean follow-up durations ranging from six months to as long as (in one study) 168 months. AP Ex. 10, at 186-87.²⁸ Additionally, two studies Dr. Ettner cited appear to be long term in that they studied patients who had undergone surgery during periods of 14 and 20 years, respectively. AP Exs. 13,²⁹ 29.³⁰ Those studies reported favorable overall results.

Dr. Ettner also testified that two studies from 1987 and 1990 used control groups and found improved psychosocial outcomes in surgery patients. Ettner Decl. at ¶¶ 28-30. In the 1990 study, she stated, MF patients were “matched for family and psychiatric histories and severity of the [GID] diagnosis” and “randomly assigned either to immediately undergo surgery, or be placed on a waiting list for two years.” *Id.* at ¶ 29, citing study at AP Ex. 23.³¹ The study found that patients who underwent surgery “demonstrated dramatically improved psychosocial outcomes, compared to the still-waiting controls” and “were more active socially and had significantly fewer psychiatric symptoms.” *Id.*; see also WPATH Br. at 8 (study found “comparative improvements in neurotic symptoms and social activity for the group receiving surgery”). Dr. Ettner described the 1990 study as the “best example of a well-controlled investigation.” Ettner Decl. at ¶ 29. Dr. Ettner also described a 1987 study comparing transsexuals who had undergone surgery with “those who had not, but were otherwise matched (control group)” as finding that “the patients who underwent surgery were better adjusted psychosocially, had improved financial circumstances, and reported increased satisfaction with sexual experiences, as compared to the unoperated group.” *Id.* at ¶ 30, citing study at AP Ex. 17.³²

²⁷ Steven Weyers, M.D., et al., *Long-term Assessment of the Physical, Mental, and Sexual Health Among Transsexual Women*, J. Sex. Med. 752-60 (2009).

²⁸ Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007).

²⁹ Ciro Imbimbo, M.D. Ph.D., et al., *A Report from a Single Institute’s 14-Year Experience in Treatment of Male-to-Female Transsexuals*, 6 J. Sex. Med. 2736-45 (2009).

³⁰ Svetlana Vujovic, M.D. Ph.D., et al., *Transsexualism in Serbia: A Twenty-Year Follow-Up Study*, 6 J. Sex. Med. 1018-23 (2009).

³¹ Charles Mate-Kole, et al., *A Controlled Study of Psychological and Social Change After Surgical Gender Reassignment in Selected Male Transsexuals*, 157 Brit. J. Psychiatry 261-64 (1990).

³² G. Kockott, M.D. & E. M. Fahrner, Ph.D., *Transsexuals Who Have Not Undergone Surgery: A Follow-Up Study*, 16 Archives of Sexual Behavior 511-22 (1987).

Nothing in the record puts into question the authoritativeness of the studies cited in the new evidence based on methodology (or any other ground). Even if questions about methodology had been raised, we would be hard pressed to find that this alone would justify our not crediting the new evidence that transsexual surgery is effective and safe. This is particularly true since the 1981 report itself suggested it might be impossible to find the kind of adequate control groups needed to assuage this criticism. See NCD Record at 18 (stating the need for adequate control groups and stating “perhaps this is impossible.”). We note that in the local coverage determination (LCD) context, CMS guidance for contractors states that the determinations “shall be based on the strongest evidence available.” CMS Medicare Program Integrity Manual (MPIM), CMS Pub. 100-08, Ch. 13, § 13.7.1.³³ While the guidance states a “preference” for “[p]ublished authoritative evidence derived from definitive randomized clinical trials or other definitive studies . . .,” it also includes as evidence meeting that standard, “[g]eneral acceptance by the medical community (standard of practice), as supported by sound medical evidence”³⁴ *Id.* In *LCD Complaint: Homeopathic Med. & Transfer Factor*, DAB No. 2315 (2010), the Board relied on that guidance when rejecting the argument that a certain type of controlled study was the sole basis on which a determination of medical necessity could be supported. The Board stated, “[a]s the [CMS guidance] explains, general acceptance in the medical community may be sufficient if it has scientific support.” DAB No. 2315, at 34. While the guidance applies to contractors, who develop LCDs but not NCDs, it is instructive here as representing CMS’s determination of the type of evidence that may support Medicare coverage. Regardless of whether the new evidence here meets the first option for meeting the evidentiary standard set forth in the guidance (and CMS does not assert that it does not), it clearly meets the second option because it indicates a consensus among researchers and mainstream medical organizations that transsexual surgery is an effective, safe and medically necessary treatment for transsexualism.

Based on the record as a whole, including the new evidence discussed above, we conclude that the AP has shown that transsexual surgery is an effective treatment option for transsexualism in appropriate cases.

³³ CMS Manuals are available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs.html>, accessed May 14, 2014.

³⁴ The guidance further provides that the “sound medical evidence” supporting this “general acceptance” should be based on “[s]cientific data or research studies published in peer-reviewed medical journals; ... [c]onsensus of expert medical opinion (i.e., recognized authorities in the field); or ... [m]edical opinion derived from consultations with medical associations or other health care experts.” MPIM § 13.7.1.

E. The new evidence indicates that the NCD's rationale for considering the surgery experimental is not valid.

The NCD asserted that transsexual surgery was considered experimental because it had not been shown to be safe and effective.³⁵ The 1981 report stated that transsexual surgery “must be considered still experimental” because “[t]he safety and effectiveness of transsexual surgery as a treatment of transsexualism is not proven and is questioned.” NCD Record at 19. As discussed above, the unchallenged new evidence indicates that transsexual surgery is a safe and effective treatment option for transsexualism in appropriate cases. Accordingly, the NCD's reasons for asserting that transsexual surgery was experimental are no longer valid.

In addition, the new evidence independently indicates that transsexual surgery is not considered experimental in a broader sense relating to its acceptance as a treatment for transsexualism. Dr. Bowers stated that “[m]any thousands of gender corrective surgeries have been performed worldwide for decades, and this treatment is in no way experimental.” Bowers Letter at 1. Dr. Hsiao testified that there is “no scientific or medical basis for [the NCD's] description of gender affirming surgeries as ‘experimental.’” Hsiao Decl. at ¶ 22. Dr. Hsiao, as noted, stated that some of the procedures involved in transsexual surgery are routinely performed in other contexts, and that surgery to create a neovagina is performed on women born MRKH. Hsiao Decl. at ¶¶ 11, 12; see Ettner Supp. Decl. at ¶ 15 (“mastectomies, hysterectomies and salpingo-oophorectomies, which are ... excluded from coverage under [the NCD] are performed frequently... when indicated for medical conditions other than gender dysphoria”).

Dr. Hsiao cited the “increasing coverage of sex affirming surgeries by private and public medical plans” and the inclusion of those surgeries “in prominent surgical text books” as showing that “gender affirming surgeries ... are the standard of care and are not experimental.” *Id.* at ¶¶ 23, 24. Dr. Hsiao cited California managed care guidance “clarifying that any attempt ‘to exclude insurance coverage of [] transsexual surgery’” would violate California law, and she stated that Vermont, Colorado, Oregon, and Washington, D.C. “have issued similar insurance directives prohibiting discrimination based on gender identity with respect to healthcare policies.” *Id.* at ¶ 25, citing Letter No. 12-K: Gender Nondiscrimination Requirements, Calif. Dep't of Managed Health Care

³⁵ “Because of the lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental.” NCD Record at 93.

(Apr. 9, 2013), Ex. A to Hsiao Decl.³⁶ “These events in the private and public sector,” Dr. Hsiao stated, “solidify what the medical community has known for years—that gender affirming surgeries to treat gender dysphoria are evidence-based, medically necessary, and the standard of care for these patients.” *Id.* at ¶ 26.

Dr. Leis stated that gender reassignment surgery “is not experimental and has been performed thousands of times with surgeons around the world and has been proven to be a medically necessary and successful treatment, saving many lives and significantly improving the lives of those who undergo this surgery.” Leis Letter at 2. Dr. Leis also stated that “[m]edical and mental health professionals who are knowledgeable and experienced in this field recognize that counseling or psychotherapy, hormone therapy and genital reassignment surgery are medically necessary treatment modalities for many individuals with [GID]” and that those therapies “are widely accepted treatments for individuals with significant [GID] in the United States and in many other countries.” *Id.* at 1. Dr. Leis also pointed to the acceptance of transsexual surgery procedures “as standard therapy by leading medical and mental health organizations” including the American Medical Association, the National Association of Social Workers, the American Psychological Association, the American Psychiatric Association, “and experts in the field belonging to” WPATH. *Id.* at 2.

HRC stated that its “Corporate Equality Index” annually surveys the “LGBT [lesbian, gay, bisexual and transgender] workplace policies” of “the Fortune 1000 list of the largest publicly traded companies along with American Lawyer Magazine’s top 200 revenue-grossing law firms” and considers “whether these organizations afford transgender-inclusive health care options through at least one firm-wide plan that covers surgical procedures.” HRC Br. at 1, 11-12. HRC stated that in 2002, “zero percent of the rated companies had such plans” but “by 2008, nineteen percent met this criterion, and by 2013, forty-two percent of companies expressly covered” care related to gender reassignment. *Id.* citing HRC Ex. 30, at 28.³⁷

Dr. Bowers, Dr. Hsiao and Dr. Ettner cited acceptance of the WPATH standards of care, which were first published in 1979 and last revised in 2011, as evidence that transsexual surgery is not experimental. Bowers Letter at 1; Hsiao Decl. at ¶ 22; Ettner Decl. at ¶¶ 38, 39; AP Ex. 7, at 165; *see also* AP Ex. 3 (AMA resolution stating that “[h]ealth experts in GID, including WPATH, have rejected the myth that such treatments are “cosmetic” or “experimental” and have recognized that these treatments can provide safe and effective treatment for a serious health condition”). The new evidence indicates that

³⁶ <http://www.dmh.ca.gov/library/reports/news/dl12k.pdf>, accessed May 14, 2014.

³⁷ HRC Corporate Quality Index (2013), available at <http://www.hrc.org/corporate-equality-index>, accessed April 25, 2014.

the WPATH standards of care have attained widespread acceptance.³⁸ See Hsiao Decl. at ¶ 22 (“the WPATH established standards of care for patients with gender dysphoria ... have been endorsed by the American Medical Association, the Endocrine Society, the American Psychological Association, and the American College of Obstetricians and Gynecologists”); AP Ex. 3 (AMA resolution stating that WPATH is “the leading international, interdisciplinary professional organization devoted to the understanding and treatment of gender identity disorders” and that its “internationally accepted Standards of Care for providing medical treatment for people with GID ... are recognized within the medical community to be the standard of care for treating people with GID”). Federal courts have recognized the acceptance of the WPATH standards of care. See, e.g., *De’lonta v. Johnson*, 708 F.3d 520, at 522-23 (4th Cir. 2013) (WPATH standards of care “are the generally accepted protocols for the treatment of GID”); *Glenn v. Brumby*, 724 F. Supp. 2d 1284, at 1289 n.4 (N.D. Ga. 2010) (“there is sufficient evidence that statements of WPATH are accepted in the medical community”).³⁹ The acceptance of the WPATH standards of care also suggests that transsexual surgery is no longer considered experimental.

In its amicus brief, WPATH cited a 2007 study that examined the results of 18 studies published between 1990 and 2006 as showing “that [sex reassignment surgery] can no longer be considered an experimental treatment” and that “it [has] bec[o]me the dominant treatment for transsexuality and the *only* treatment that has been evaluated empirically.” WPATH Br. at 7-8, citing AP Ex. 10, at 214-15.⁴⁰

We note that in addition to stating that transsexual surgery was experimental, the NCD and the 1981 report stated that transsexual surgery was “controversial.” NCD Record at 18 (1981 report stating that “[o]ver and above the medical and scientific issues, it would also appear that transsexual surgery is controversial in our society”). The AP and the new evidence dispute the relevance of this statement. The AP objected that this point relies on two “polemics” that are “are either completely unscientific or fall far outside the scientific mainstream,” and Dr. Ettner stated that the views expressed therein “fall far outside the mainstream psychological, psychiatric, and medical professional consensus,

³⁸ WPATH was “formerly the Harry Benjamin International Gender Dysphoria Association.” Ettner Decl. at ¶ 6. Harry Benjamin, M.D. “was an endocrinologist who in conjunction with mental health professionals in New York did pioneering work in the study of transsexualism.” *O’Donnabhain v. Comm’r of Internal Revenue*, 134 T.C. 34, 37 n.8 (2010). The 1981 report cites a 1966 study by Dr. Benjamin finding a positive outcome from MF transsexual surgery as “perhaps the first report” on transsexual surgery “in the literature.” NCD Record at 15, 21.

³⁹ The general acceptance of a set of standards of care for the treatment of transsexuals appears to render invalid one of the 1981 report criticisms of the studies it discussed, that “therapeutic techniques are not standardized.” NCD Record at 18.

⁴⁰ Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007).

and call into question the objective reasonableness of the NCD.” AP Statement at 15-16; Ettner Supp. Decl. at ¶¶ 17-18. CMS has not asserted that the Board’s decision may be based on factors “over and above the medical and scientific issues” involved. Considerations of social acceptability (or nonacceptability) of medical procedures appear on their face to be antithetical to Medicare’s “medical necessity” inquiry, which is based in science, and such considerations do not enter into our decision that the NCD is not valid.

For the reasons stated above, we conclude that citing the alleged “experimental” nature of transsexual surgery as a basis for noncoverage of all transsexual surgery is not reasonable in light of the unchallenged new evidence and contributes to our conclusion that the NCD is not valid.

Conclusion

For the reasons explained above, we conclude that the AP has shown that NCD 140.3 is not valid under the reasonableness standard.

/s/

Leslie A. Sussan

/s/

Constance B. Tobias

/s/

Sheila Ann Hegy
Presiding Board Member

ATTACHMENT TO DECISION NO. 2576

Overview of the Scientific Literature in the New Evidence

We provide below brief summaries of key findings in some of the studies submitted and reviewed by the Board as new evidence. The key findings in the remaining studies reviewed by the Board (also as new evidence) do not differ in any way material to our decision.

Jan Eldh, et al., *Long Term Follow Up After Sex Reassignment Surgery*, 31 Scand. J. Plast. Reconstr. Surg. Hand Surg. 39-45 (1997), AP Ex. 9. This study was a “long-term follow up of 136 patients operated on for sex reassignment ... to evaluate the surgical outcome” that divided MF and FM patients into “two groups according to the surgical technique: those operated on before 1986 and those operated on from 1986–1995.” The study found that after 1985 “the outcome of surgery became much better not only because of changes in management but also because of improvements in surgical technique, preoperative planning, and postoperative treatment,” that “[m]odern surgical techniques can give good aesthetic and functional results” and that “[p]ersonal and social instability before operation correlated with an unsatisfactory outcome of sex reassignment.” *Id.* at 39, 44, 45.

Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges*, 18 Ann. Rev. Sex Res. 178-224 (2007), AP Ex. 10. This study examined results of 18 international studies published between 1990 and 2006 that reported follow-up data of at least one year from 807 persons who had undergone sex reassignment surgery (193 FM, 614 MF). The purpose of this study was to update and assess the current validity of a conclusion in a 1990 article (based itself on review of 11 studies following post-operation) that transsexual surgery is an effective treatment for the alleviation of gender disorder in adults. This study concluded that “[d]espite methodological shortcomings of many of the studies . . . SRS is an effective treatment for transsexualism and the only treatment that has been evaluated empirically with large clinical case series” and that the “conclusion that SR [sex reassignment] is the most appropriate treatment to alleviate the suffering of extremely gender dysphoric individuals still stands: 96% of the persons who underwent SRS were satisfied and regret was rare.” The authors noted that the methodologies and designs of later studies were improved but that true randomized control studies are not feasible, and might be unethical for SRS. *Id.* at 178, 185, 215-16.

Ciro Imbimbo, M.D. Ph.D., et al., *A Report from a Single Institute’s 14-Year Experience in Treatment of Male-to-Female Transsexuals*, 6 J. Sex. Med. 2736-45 (2009), AP Ex. 13. This study’s aim was “to arrive at a clinical and psychosocial profile of male-to-female transsexuals in Italy through analysis of their personal and clinical experience and evaluation of their postsurgical satisfaction levels SRS.” From January 1992 to September 2006, 163 MF patients who had undergone SRS were asked to complete

patient satisfaction questionnaires. The study concluded that the “relatively high satisfaction level” was the result of a combination of “competent surgical skills, a well-conducted preoperative preparation program, and adequate postoperative counseling” Although postoperative pain and required revision surgeries were reported, the study found that 94% were satisfied with their post-surgical status and did not report regret. *Id.* at 2736, 2740, 2743.

Ladislav Jarolim, et al., *Gender Reassignment Surgery in Male-to-Female Transsexualism: A Retrospective 3-Month Follow-up Study with Anatomical Remarks*, 6 J. Sex. Med. 1635-44 (2009), AP Ex. 14. This study aimed “[t]o evaluate the results of surgical reassignment of genitalia in male-to-female transsexuals” by measuring “[s]exual functions and complications 3 months after surgery.” The study followed 134 patients who had undergone surgical procedures between 1992 and 2008 and described the evolution in surgical techniques since the 1950s. Although the study noted potential complications and risks specific to SRS (“such as impairment of urinary continence, fecal continence, intestinal fistula, urinary fistula, and necrosis of the skin graft”), it concluded that “[s]urgical conversion of the genitalia is a safe and important phase of the treatment of male-to-female transsexuals.” It also concluded that “[a]n increasing number of patients undergo this treatment because of the extensive progress in surgery involving the genitals and urethra” and that “[f]or male transsexuals, surgery can provide a cosmetically acceptable imitation of female genitals that enables coitus with orgasm.” *Id.* at 1635-36, 1642-43.

Annika Johansson, et al., *A Five-Year Follow-Up Study of Swedish Adults with Gender Identity Disorder*, 39 Arch. Sex. Behav. 1429-37 (2010), AP Ex. 15. This study evaluated from the perspective of both clinicians and patients the outcome of sex reassignment of “42 [MF and FM] transsexuals [who] completed a follow-up assessment after 5 or more years in the process or 2 or more years after completed sex reassignment surgery.” It found that “the outcome was very encouraging from both perspectives ... with almost 90% enjoying a stable or improved life situation at follow-up and only six out of 42 (according to the clinician) with a less favorable outcome.” *Id.* at 1429, 1436.

G. Kockott, M.D. & E. M. Fahrner, Ph.D., *Transsexuals Who Have Not Undergone Surgery: A Follow-Up Study*, 16 Archives of Sexual Behavior 511-22 (1987), AP Ex. 17. This single-clinic study compared 26 transsexuals who sought but did not undergo surgery with 32 who did; psychosocial adjustment of those who delayed surgery did not improve from the time of diagnosis to follow-up while statistically significant positive changes in gender role, sexual, and socioeconomic adjustment were seen in transsexuals who had had surgery. *Id.* at 511, 517-19, 521.

Anne A. Lawrence, *Patient-Reported Complications and Functional Outcomes of Male-to-Female Sex Reassignment Surgery*, 35 Arch. Sex. Behav. 717-27 (2006), AP Ex. 21. This study “examined preoperative preparations, complications, and physical and

functional outcomes of [MF SRS] based on reports by 232 patients, all of whom underwent penile-inversion vaginoplasty and sensate clitoroplasty, performed by one surgeon using a consistent technique,” who were surveyed a mean of three years after surgery. The study found that “[r]eports of significant surgical complications were uncommon,” although one third had urinary stream problems, and that “[o]n average, participants expressed high levels of satisfaction with nearly all of the specific physical and functional outcomes of SRS.” *Id.* at 717, 719, 724.

Maria Inês Lobato, et al., *Follow-Up of Sex Reassignment Surgery in Transsexuals: A Brazilian Cohort*, 35 Arch. Sex. Behav. 711-15 (2006), AP Ex. 22. This small study examined the “impact of sex reassignment surgery on satisfaction with sexual experience, partnerships, and relationship with family members in ... 19 patients who received sex reassignment between 2000 and 2004.” The results “indicate[d] that SRS had a positive effect on different dimensions of the patients’ lives in all three aspects analyzed: sexual relationships, partnerships, and family relationships.” *Id.* at 711-12, 714.

Charles Mate-Kole, et al., *A Controlled Study of Psychological and Social Change after Surgical Gender Reassignment in Selected Male Transsexuals*, 157 Brit. J. Psychiatry 261-64 (1990), AP Ex. 23. This study reviewed 40 patients accepted for gender reassignment surgery, randomly assigned to have surgery early or later such that only half had had surgery by the time of a follow-up two years later. The study found that “[a]lthough the groups were similar initially, significant differences between them emerged at follow-up” Patients who received surgery were “seen to improve significantly as far as neurotic symptoms are concerned and to become more socially active” in comparison with the patients who had not yet received surgery. *Id.* at 261, 264.

Friedemann Pfafflin & Astrid Junge, *Sex Reassignment: Thirty Years of International Follow-Up Studies After Sex Reassignment Surgery: A Comprehensive Review 1961-1991* (Roberta B. Jacobson & Alf B. Meier trans., 1998) (1992), AP Ex. 25. This overview was completed in 1992 and published in English in 1998. It reviewed “30 years of international follow-up studies of approximately two thousand persons who had undergone sex reassignment surgery,” including “more than 70 individual studies and eight published reviews from four continents.” In general, more frequent and severe complications were found in the earlier years covered than in later reports. The overview concluded that “[s]ex reassignment, properly indicated and performed, has proven to be a valuable tool in the treatment of individuals with transgenderism,” that “gender reassigning treatments are effective” and that “the treatment that includes the whole process of gender reassignment is effective.” *Id.* at unnumbered pages 1, 45, 66-67.

Yolanda L.S. Smith, et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals*, 35 Psychol. Med. 89-99 (2005), AP Ex. 27. This study evaluated “outcomes of sex reassignment, potential differences between subgroups

of transsexuals, and predictors of treatment course and outcome” in 162 adults (104 MF, 58 FM). The study found that “[a]fter treatment the group was no longer gender dysphoric,” had “improved in important areas of function, that 1-4 years after surgery, SR appeared therapeutic and beneficial . . . [and that] the vast majority expressed no regrets about their SR.” The study further concluded “that sex reassignment is effective” but that “clinicians need to be alert for non-homosexual male-to-females with unfavourable psychological functioning and physical appearance and inconsistent gender dysphoria reports, as these are risk factors for dropping out and poor post-operative results.” *Id.* at 89, 91, 96.

Svetlana Vujovic, M.D., Ph.D., et al., *Transsexualism in Serbia: A Twenty-Year Follow-Up Study*, 6 J. Sex. Med. 1018-23 (2009), AP Ex. 29. This study [a]imed to “describe a transsexual population seeking sex reassignment treatment in Serbia” by analyzing “data collated over a period of 20 years” from 147 transsexuals “applying for sex reassignment” of whom SRS was performed in 83% of MF and in 77% of MF patients. The study concluded that “in our population, there were no cases who regretted sex reassignment treatment,” which was attributed to diagnostic procedures used and the “young [adult] age at which our subjects embarked on treatment.” *Id.* at 1018-20, 1022.

Steven Weyers, M.D., et al., *Long-term Assessment of the Physical, Mental, and Sexual Health Among Transsexual Women*, J. Sex. Med. 752-60 (2009), AP Ex. 30. This study [a]imed “[t]o gather information on physical, mental, and sexual well-being, health-promoting behavior and satisfaction with gender-related body features of [49] transsexual women [MF] who had undergone SRS” with mean interval since vaginoplasty of 75.46 months. The study found that “sample . . . functions well after surgery on a physical, emotional, psychological and social level” and that “[o]nly with respect to sexuality do transsexual women appear to suffer from specific difficulties, especially concerning arousal, lubrication and pain.” *Id.* at 752, 754, 759.