No. 22-11707

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

PAUL A. EKNES-TUCKER, et al.,
Plaintiffs-Appellees,

&

UNITED STATES OF AMERICA
Intervenor-Plaintiff-Appellee,

v.

GOVERNOR OF THE STATE OF ALABAMA, et al.,
Defendants-Appellants.

On Appeal from the United States District Court
for the Middle District of Alabama
Case No. 2:22-cv-184-LCB

APPELLANTS' APPENDIX VOLUME IV OF XIII

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UNITED STATES DISTRICTCOURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity As Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official Capacity as District Attorney for Jefferson County.

Defendants

CIVIL ACTION # 2:22-cv-00184-LCB-SRW

Expert Report of Paul W. Hruz, M.D., Ph.D.

Pursuant to 28 U.S.C. 1746, I declare:

1. RETAINED AS EXPERT WITNESS - VITAE: I have been retained by counsel for Defendants as an expert witness in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this declaration. My professional background, experience, and publications are detailed in my curriculum vitae. A true and accurate copy of my CV is attached as Exhibit A to this declaration.

2. EDUCATION - ACADEMIC APPOINTMENTS: I received my Doctor of Philosophy degree from the Medical College of Wisconsin in 1993. I received my Medical Degree from the Medical College of Wisconsin in 1994. I am an Associate Professor of Pediatrics in the Division of Pediatric Endocrinology and Diabetes at Washington University School of Medicine. I also have a secondary appointment as Associate Professor of Cellular Biology and Physiology in the Division of Biology and Biological Sciences at Washington University School of Medicine. I served as Chief of the Division of Pediatric Endocrinology and Diabetes at Washington University from 2012-2017. I served as the Director of the Pediatric Endocrinology Fellowship Program at Washington University from 2008-2016. I am currently serving as Associate Fellowship Program Director at Washington University in St. Louis.

3. HISTORY OF BOARD CERTIFICATIONS: I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Missouri since 2000. I also have a temporary license to practice telemedicine in Illinois during the COVID-19 pandemic. My professional memberships include the American Diabetes Association, the Pediatric Endocrine Society, and the Endocrine Society.

4. SCIENTIFIC PUBLICATIONS IN PEER REVIEWED JOURNALS: I have published 60 scholarly articles over my academic career spanning over two decades. This includes

peer-reviewed publications in the leading journals in the fields of metabolism, cardiology, HIV, and ethics including the Gastroenterology, Circulation, Diabetes, Science Signaling, the Journal of Biological Chemistry and FASEB Journal. See my current Curriculum Vitae attached as Exhibit A.

5. EDITORIAL DUTIES - RESEARCH GRANTS: I have served as a Reviewer for a number of leading science journals in relevant fields including the Journal of Clinical Endocrinology and Metabolism, the Journal of Biological Chemistry, Diabetes, Scientific Reports and PlosOne. I have received over 4.6 million dollars in governmental and non-governmental funding for scientific research including grants from the National Institutes of Health, the American Diabetes Association, The American Heart Association, the March of Dimes, and the Harrington Discovery Institute. I am a member of the Alpha Omega Alpha Medical Honor Society and have received the Armond J. Quick Award for Excellence in Biochemistry, the Eli Lilly Award for Outstanding Contribution to Drug Discovery, and the Julio V. Santiago Distinguished Scholar in Pediatrics Award.

6. CLINICAL EXPERIENCE: During the more than 20 years that I have been in clinical practice, I have participated in the care of hundreds of infants and children, including adolescents, with disorders of sexual development. I was a founding member of the multidisciplinary Disorders of Sexual Development (DSD) program at Washington University. I continue to contribute to the discussion of complex cases and the advancement of research priorities in this field. In the care of these patients, I have acquired expertise in the understanding and management of associated difficulties in gender identification and gender transitioning treatment issues. I have trained and/or supervised hundreds of medical students, residents and clinical fellows in the practice of medicine.

7. PREVIOUS LEGAL CASES AS AN EXPERT WITNESS: Related to the litigation of issues of sex and gender, I have been designated as an expert witness in Joaquín Carcaño et al vs. Patrick McCrory (United States District Court, M.D. North Carolina), Jane Doe vs Board of Education of the Highland School District (United States District Court For the Southern District of Ohio Eastern Division, Case No. 2:16-CV-524), Ashton Whitaker vs. Kenosha Unified School District (United States District Court Eastern District of Wisconsin, Civ. Action No. 2:16-cv-00943), Adams vs. the School Board of St. John's County (United States District Court Middle District Of Florida Jacksonville Division, Case No. 3:17-cv-739-J-32JBT), Terri Bruce vs State of South Dakota (The United States District Court District of South Dakota Western Division, Case No. 17-5080), Kadel vs. Falwell (The United States District Court For The Middle District Of North Carolina, Case No.: 1:19-cv-272-LCB-LPA), Brandt v Rutledge (The United States District Court Eastern District of Arkansas Central Division, Case No. 4:21-CV-00450-JM), and Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children. Only in the last case did I testify at trial. I have also served as a science consultant or subjected written testimony for court cases in Canada (B.C. Supreme Court File No. E190334) and Great Britain (Bell v Tavistock).

8. COMPENSATION: I am being compensated at an hourly rate for actual time devoted, at the rate of $400 per hour including report drafting, travel, testimony, and consultation. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

9. CONSULTS-DISCUSSIONS REGARDING THE RELEVANT SCIENCE and CLINICAL ISSUES: In my role as a scientist and as the Director of the Division of Pediatric Endocrinology at Washington University, I extensively studied the existing scientific research

literature related to the incidence, potential etiology, and treatment of gender dysphoria as efforts were made to develop a Transgender Medicine Clinic at Saint Louis Children's Hospital. I have participated in local and national meetings where the endocrine care of children with gender dysphoria has been discussed in detail and debated in depth. I have met individually and consulted with several pediatric endocrinologists (including Dr. Norman Spack) and other professionals specializing in sexual health (including Eli Coleman) who have developed and led transgender programs in the United States. I have also consulted with, met with, and had detailed discussions with dozens of parents of children with gender dysphoria to understand the unique difficulties experienced by this patient population. I continue to evaluate the ongoing experimental investigation of this condition. I am frequently consulted by other medical professionals to help them understand the complex medical and ethical issues related to this emerging field of medicine.

10. In my opinion, there is a serious lack of quality scientific evidence regarding the safety and efficacy of gender affirming medical interventions for individuals who exercise sex discordant gender identity. Use of such medical interventions remains a highly controversial and largely experimental approach.

Pediatric patients referred to our practice for the evaluation and treatment of gender dysphoria are cared for by an interdisciplinary team of providers that includes a psychologist and pediatric endocrinologist who have been specifically chosen for this role based upon a special interest and professional knowledge and training in this rare patient population. Due to the documented, important, ethical concerns regarding the safety, efficacy, and scientific validity of controversial, unproven, and experimental treatment paradigms, I have not personally engaged in the delivery of gender affirming medical interventions to children with gender dysphoria. Given the

unproven long-term benefits and the well-documented risks and harms of "transitioning" children, I decline to participate in such experimental treatments until the science has proven that the relative risks and benefits of this approach warrant such procedures.

My decision is strengthened by the knowledge that the vast majority of children who report gender dysphoria will, if left untreated, grow out of the problem — a natural coping-developmental process — and willingly accept their biological sex. Despite differences in country, culture, decade, follow-up length and method, multiple studies have come to a remarkably similar conclusion: Very few gender dysphoric children still want to transition by the time they reach adulthood. Many turn out to have been struggling with sexual orientation issues rather than Gender Discordant "transgender" identity. The exact number of children who experience realignment of gender identity with biological sex by early adult life varies by study. Estimates within the peer reviewed published literature range from 50-98%, with most reporting desistance in approximately 85% of children prior to the widespread adoption of the "gender affirmation only" approach. Thus, desistance (i.e., the child accepting their natal, biological sex identity and declining "transitioning" treatments) is the outcome for the vast majority of affected children who are not actively encouraged to proceed with sex-discordant gender affirmation. Since there are no reliable assessment methods for identifying the small percentage of children with persisting sex-gender identity discordance from the vast majority who will accept their biological sex, and since puberty blocking treatments, hormone transition treatments, and surgical transition treatments are all known to have potentially life-long devastating, negative effects on patients, I and many colleagues view it as unethical to treat children with an unknown future by using experimental, aggressive, and intrusive gender affirming medical interventions. See J. Cantor,

Ph.D. summary of multiple research studies at http://www.sexologytoday.org/2016/01/do-trans-kids-stay-trans-when-they-grow_99.html, and other publications reviewed in detail below).

11. PEER-REVIEWED, PUBLISHED RESEARCH IN CREDIBLE SCIENCE-MEDICAL JOURNALS: My opinions as detailed in this declaration are based upon my knowledge and direct professional experience in the subject matters discussed. The materials that I have relied upon are the same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject including hundreds of published, peer reviewed scientific research (and professional) articles. As discussed in detail in this declaration, the extant published literature on the use of puberty blockers, cross-sex hormones and gender affirming surgeries are based, almost entirely, upon studies with major methodological limitations (see Hruz, P. W. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q* 87, 34-42, doi:10.1177/0024363919873762 (2020). This includes:

- Significant recruitment biases including internet based convenience sampling
- Relatively small sample sizes for addressing a condition that is likely to be multi-factorial
- Short term follow up
- Lack of randomization to different treatment arms
- Failure to even consider alternate hypotheses
- Failure to include proper control groups and, in many studies NO control group at all
- Reliance on cross sectional sampling that may identify associations, but cannot establish causal relationships between intervention and outcome.

- A high rate of patients lost to follow up in longitudinal analyses which is relevant to questions of regret, desistance and completed suicide.
- Biased interpretation of study findings with a goal of validating *a priori* conclusions rather than seeking evidence to disprove the null hypothesis
- Ignoring starkly contradictory research documenting the lack of effectiveness of "transitioning" procedures, the low quality of research in this area, and the ongoing contentions and disagreements over this highly controversial, experimental medical field

12. PUBLIC DISCLOSURES OF THE METHODOLOGICAL FAILURES OF GENDER TRANSITIONING MEDICAL INTERVENTIONS: In addition to peer reviewed published research articles related to gender affirming medical interventions (see specific citations below), I also cite a wide variety of evidence documenting the recent, very public, disclosures of the multiple and serious methodological errors, failures, and defects of "transitioning treatment" research. Specific examples include:

THE BRANSTROM LONG-TERM TREATMENT OUTCOME STUDY: The historic Branstrom report is a peer reviewed, published, scientific journal article that documents a long-term treatment (10+ years) outcome research investigation testing the effects of hormonal and surgical "transitioning" treatments on patients. This historic research found *no reliable benefits from these disfiguring-sterilizing "treatments"* as well as evidence suggesting *increased* suicide attempts and anxiety disorders following the "gender transitioning" treatments. In addition, detailed methodological critiques discovered significant research errors by the authors that appear to support the investigative theory that the authors had initially attempted to manipulate

and misreport the findings of the study. (See, very detailed notes and review below with multiple citations). The authors ultimately recanted their initial misreporting and agreed that their study produced *no reliable evidence of benefits* for gender reassignment hormone and surgical treatments. The Branstrom study is truly a devastating and historic blow to the WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH's (WPATH) "treatment guidelines" and to the financially lucrative transgender "transitioning" treatment industry. Together with other evidence, this historic investigation has helped to generate a profound collapse of support for these experimental procedures across Europe. See *Correction of a Key Study: No Evidence of "Gender-Affirming" Surgeries Improving Mental Health.* https://segm.org/ajp_correction_2020. Accessed 29 June 2021. , Van Mol, A., Laidlaw, M., Grossman, M., & McHugh, P. (2020). *Gender-Affirmation Surgery Conclusion Lacks Evidence.* Am. J. Of Psych., 177(8), 765-766. (see detailed review below).

NATIONAL FINLAND REVIEW RECOMMENDS SUSPENDING TRANSITIONING TREATMENTS FOR CHILDREN AS EXPERIMENTAL and of UNCERTAIN BENEFIT: A National Science Review in FINLAND carefully examined all relevant science and suspended transition treatments for minors under age 16. See One Year Since Finland Broke with WPATH "Standards of Care." https://segm.org/Finland_devites_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors. The official review recommends that psychotherapy should be the first line of treatment for gender dysphoric youth. See 2020 Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland) Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors, "Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty…. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and

treatment of possible comorbid psychiatric disorders. … No gender confirmation surgeries are performed on minors." … "Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system"… "there are no medical treatments (for transitioning) that can be considered evidence-based… In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development…. A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options. For children and adolescents, these factors are key reasons for postponing any interventions until adulthood…. In light of available evidence, gender reassignment of minors is an experimental practice." See One Year Since Finland Broke with WPATH "Standards of Care." https://segm.org/Finland_devites_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors.

SWEDEN'S FLAGSHIP KAROLINSKA HOSPTIAL SUSPENDS TRANSITIONING TREATMENTS FOR CHILDREN UNDER 16 AND REQUIRES RESEARCH OVERSIGHT FOR PATIENTS UNDER 18: In Sweden, the world-renowned Karolinska Hospital reviewed the current research and suspended pediatric gender transitions for patients under 16 outside of experimental, monitored clinical trials settings as of May 2021. Treatment will focus on psychotherapy and assessment. See Sweden's Karolinska Ends All Use of Puberty Blockers and Cross-Sex Hormones for Minors Outside of Clinical Studies. https://segm.org/Sweden_ends_use_of_Dutch_protocol. See also, Karolinska Policy Change K2021-3343 March 2021 (in English).pdf; Karolinska Hospital Ends the Use of Puberty Blockers for patients under 16: New policy statement from the Karolinska Hospital. The "Dutch protocol" for treating gender dysphoric minors has been discontinued over concerns of medical harm and uncertain benefits. This new Swedish policy is consistent with Finland's recently revised guidelines and changes in England's policies as well as the Arkansas legislation in the U.S. All have been changed to prioritize psychological interventions and social support in contrast to medical interventions, particularly for youth with no young childhood history of gender dysphoria (presently the most common patient presentation)" See Society for Evidence Based Gender Medicine Press Release at https://segm.org/Sweden_ends_use_of_Dutch_protocol and Karolinska Policy Change K2021-3343 March 2021 (English, unofficial translation).pdf Karolinska Guideline K2021-4144 April 2021 (English, unofficial translation).pdf

SWEDEN National review documents the lack of quality research in this controversial field. See Sweden Policy Review, Gender dysphoria in children and adolescents: an inventory of the literature, SBU Policy Support no 307, 2019 (https://www.sbu.se/307e) "This report

was commissioned by the Swedish government and is a scoping review of the literature on gender dysphoria in children and adolescents. The report can be a basis for further evaluation of risk of bias and evidence."…" The Swedish national review reported: "No relevant randomized controlled (treatment outcome) trials in children and adolescents were found." The review also reported … "Conclusions: — We have not found any scientific studies which explains the increase in incidence in children and adolescents who seek the heath care because of gender dysphoria — We have not found any studies on changes in prevalence of gender dysphoria over calendar time, nor any studies on factors that can affect the societal acceptance of seeking for gender dysphoria. — There are few studies on gender affirming surgery in general in children and adolescents and only single studies on gender affirming genital surgery. — Studies on long-term effects of gender affirming treatment in children and adolescents are few, especially for the groups that have appeared during the recent decennium….— Almost all identified studies are observational, some with controls and some with evaluation before and after gender affirming treatment. No relevant randomized controlled trials in children and adolescents were found. … We have not found any composed national information from Sweden on: — the proportion of those who seek health care for gender dysphoria that get a formal diagnosis nor — the proportion starting endocrine treatment to delay puberty nor — the proportion starting gender affirming hormonal treatment nor — the proportion subjected to different gender affirming surgery."

UK RESEARCHERS, COURTS, and OTHER REVIEWERS HIGHLIGHTED THE PAUCITY OF RESEARCH, LIMITATIONS, DEFECTS, and RISKS IN THE STILL EXPERIMENTAL "GENDER TRANSITIONING" TREATMENT FIELD:

The British official medical review office (NICE) published reports on transitioning science. See Cohen, D. and Barnes, H., BBC, "Evidence for puberty blockers use very low, says

NICE" … "The evidence for using puberty blocking drugs to treat young people struggling with their gender identity is "very low", an official review has found. The National Institute of Health and Care Excellence (NICE) said existing studies of the drugs were small and "subject to bias and confounding." The assessment of the evidence into the drugs was commissioned by NHS England. It is part of a review into gender identity services for children and young people. See https://arms.nice.org.uk/resources/hub/1070905/attachment. The NICE review noted it was difficult to draw conclusions from existing studies because of the way they had been designed. They were "all small" and did not have control groups, which are used to directly compare the effect of different treatments. There were other issues with the studies too, such as not describing what other physical and mental health problems a young person may have alongside gender dysphoria.

NICE also reviewed the evidence base for cross-sex hormones. See https://arms.nice.org.uk/resources/hub/1070871/attachment. The review found the evidence of clinical effectiveness and safety of cross-sex hormones was also of "very low" quality. "Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria," NICE said. Both documents were prepared by NICE in October 2020 and will now help inform Dr. Hilary Cass's independent review into NHS gender identity services for children and young people. See also Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. medRxiv 2020.12.01.20241653; doi:https://doi.org/10.1101/2020.12.01.20241653. This British study conclusion noted: "We found no evidence of change (no improvement) in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-re-

port (YSR) of overall problems, internalizing or externalizing problems or self-harm…." Puberty blockers used to treat children aged 12 to 15 who have severe and persistent gender dysphoria had no significant effect on their psychological function, thoughts of self-harm, or body image, a study has found. However, as expected, the children experienced reduced growth in height and bone strength by the time they finished their treatment at age 16. See, also Dyer, C. Puberty blockers: children under 16 should not be referred without court order, says NHS England. BMJ2020;371:m4717.doi:10.1136/bmj.m4717 pmid:33268453. See, Dyer, C., Puberty blockers do not alleviate negative thoughts in children with gender dysphoria, finds study, BMJ 2021;372:n356 doi: https://doi.org/10.1136/bmj.n356 (Published 08 February 2021); see also Dyer, C. Puberty blockers do not alleviate [suicidal] negative thoughts in children with gender dysphoria, finds study. BMJ 372, n356, doi:10.1136/bmj.n356 (2021). https://www.medrxiv.org/content/10.1101/2020.12.01.20241653v1 BBC summary: https://www.bbc.com/news/uk-55282113journal.pone.0243894. pmid:33529227. See also, "Tavistock's Experimentation with Puberty Blockers: Scrutinizing the Evidence," TransgenderTrend.com, March 5, 2019. Regarding the UK's Tavistock and Portman NHS Trust's Gender Identity Development Service's experimental trial of puberty blockers for early teenagers with gender dysphoria. Oxford's Professor Michael Biggs wrote, "To summarize, GIDS launched a study to administer experimental drugs to children suffering from gender dysphoria."… "After a year on GnRHa [puberty blockers] children reported greater self-harm, and girls experienced more behavioral and emotional problems and expressed greater dissatisfaction with their body—so puberty blockers actually exacerbated gender dysphoria."

See also Griffin, L., Clyde, K., Byng, R., Bewley, S., Sex, gender and gender identity: a re-evaluation of the evidence. BJPsych Bulletin (2020) doi:10.1192/bjb.2020.73, Cambridge University Press, 21 July 2020, As Griffin, et al discussed, "As there is evidence that many psychiatric disorders persist despite positive affirmation and medical transition, it is puzzling why transition would come to be seen as a key goal rather than other outcomes, such as improved quality of life and reduced morbidity. When the phenomena related to identity disorders and the evidence base are uncertain, it might be wiser for the profession to admit the uncertainties". … "In addition, Griffin et al wrote: "Transgender support groups have emphasized the risk of suicide. After controlling for coexisting mental health problems, studies show an increased risk of suicidal behaviour and self-harm in the transgender population, although underlying causality has not been convincingly demonstrated. (See 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 2016; 28: 58–69.). In sum, political activists and too many providers have used a fear of suicide to push experimental unproven, hazardous treatments.

REVIEW OF WPATH: A 2021 review found WPATH standards "incoherent." See Dahlen, Sara, et al. "International Clinical Practice Guidelines for Gender Minority/Trans People: Systematic Review and Quality Assessment." BMJ Open, vol. 11, no. 4, Apr. 2021, p. e048943. Both WPATH and Endocrine Society guidelines have recently been assessed for quality by a systematic review, which found them to be of low quality. Specific to WPATH, the reviewers noted the difficulty of even extracting clear recommendations, describing the WPATH guidelines as "incoherent." Standards of care should provide practitioners with evidence-based standards by which they may reliably inform the patient of projected outcomes, and do so with a

known error rate. Such data is the starting point for obtaining informed consent, which is not provided by either of these guidelines.

THE INDEPENDENT REVIEW OF GENDER IDENTITY SERVICES FOR CHILDREN AND YOUNG PEOPLE: INTERIM REPORT by Dr. Cass in the UK published in February 2022 concluded that "Evidence on the appropriate management of children and young people with gender incongruence and dysphoria is *inconclusive* both nationally and internationally." Dr. Cass notes that "There is lack of consensus and open discussion about the nature of gender dysphoria and therefore about the appropriate clinical response." (see https://cass.independent-review.uk/publications/interim-report/)

THE SOCIETY FOR EVIDENCE BASED GENDER MEDICINE (SEGM) REVIEW SUMMARIZES THE HEALTH RISKS of TRANSITIONING: Consistent with changes in Sweden, Finland, England, and Arkansas, SEGM published a research summary documenting the serious health risks of "transitioning treatments" compared to the well-known lack of evidence of reliable benefits for such treatments. See Science Studies – Health Risks of Medical and Surgical Gender Reassignment." SEGM at. https://www.segm.org/studies.

EXPERTS ARE CONCERNED WITH UNEXPLAINED DEMOGRAPHIC SHIFTS IN PATIENTS FOR WHOM PREVIOUS RESEARCH IS OF UNKNOWN USEFULNESS — For decades transgender patients were mostly older adults or very young boys. Over the last few years a tsunami of teenaged girls has flipped the demographics of transgender patients—now up to 7 to 1 teen girls. Many experts have noted that the previous research on trans patients cannot be relied upon when the patient group has so rapidly and mysteriously been transformed. In sum, the newly presenting cases are vastly overrepresented by adolescent females, the majority of whom also have significant mental health problems and neurocognitive comorbidities such as

autism-spectrum disorder or ADHD. See de Graaf, Nastasja M., and Polly Carmichael. "Reflections on Emerging Trends in Clinical Work with Gender Diverse Children and Adolescents." Clinical Child Psychology and Psychiatry, vol. 24, no. 2, Apr. 2019, pp. 353–64. The most recent evidence supports the emerging theory of social contagion as estimates of gender dysphoria-transgenderism are rocketing upwards from 1 in 10,000 to "the number of U.S. transgender-identified youth may be as high as 9%." See Kidd, Kacie M., et al. "Prevalence of Gender-Diverse Youth in an Urban School District." Pediatrics, vol. 147, no. 6, June 2021, p. e2020049823. This unexplained, radical transformations of demographics does not happen in actual illnesses (cancer, heart disease, anxiety disorders, etc), but is tragically consistent with previous mental health system disasters such as the once very rare "multiple personality disorder" and "recovered repressed memory" patients that radically increased in the 1990s. Dr. Thomas Steensma, a prominent investigator of the Dutch protocol—the original model for transitioning treatments—has recently noted that "[w]e don't know whether studies we have done in the past can still be applied to this time," specifically because of the unexplained surge in female adolescents reporting gender dysphoria. "Many more children are registering, but also of a different type… Suddenly there are many more girls applying who feel like a boy... now there are three times as many females as males." He concluded with the warning that "[w]e conduct structural research in the Netherlands. But the rest of the world is blindly adopting our research." See https://www.voorzij.nl/more-research-is-urgently-needed-into-transgender-care-for-young-people-where-does-the-large-increase-of-children-come-from/

A MARCH 2021 STUDY—WITH THE LARGEST SAMPLE YET—IS CONSISTENT WITH THE NEW DIRECTION OF FINLAND, SWEDEN, THE UK, and FRANCE—SHOWS THAT MOST YOUNG GENDER DYSPHORIA CHILDREN GROW

OUT OF THE PROBLEM WITH NO MEDICAL INTERVENTION. See Devita Singh1, Susan J. Bradley 2 and Kenneth J. Zucker, Frontiers in Psychiatry, March 2021, Volume 12, Article 632784, www.frontiersin.org. "Watchful Waiting" is the recommended treatment: In the past, 67% of children meeting the diagnostic criteria for gender dysphoria no longer had the diagnosis as adults, with an even higher, 93% rate of natural resolution of gender-related distress for the less significantly impacted cases. See also, e.g. Zucker, K. J. (2018). The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). International Journal of Transgenderism, 19(2), 231–245.

THE COCHRANE REVIEW FOUND INSUFFICIENT EVIDENCE OF BENEFITS: The widely respected Cochrane Review examined hormonal treatment outcomes for male-to-female transitioners over 16 years. They found "insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition." It is remarkable that decades after the first transitioned male-to-female patient, quality evidence for the benefit of transitioning is still lacking. See Haupt, C., Henke, M. et. al., Cochrane Database of Systematic Reviews Review - Intervention, Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women, 28 November 2020 and https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013138.pub2/full.

13. A reasonable understanding of relative risk versus benefit for medical products or procedures is a fundamental obligation in providing appropriate clinical care. This is the bedrock standard of "evidence based medical practice." As detailed throughout this declaration, this foundational standard has never been met by the gender transition industry. As noted by Levine et al. "The risks of gender-affirmative care are ethically managed through a properly conducted

informed consent process. Its elements-deliberate sharing of the hoped-for benefits, known risks and long-term outcomes, and alternative treatments-must be delivered in a manner that promotes comprehension. The process is limited by: erroneous professional assumptions; poor quality of the initial evaluations; and inaccurate and incomplete information shared with patients and their parents" (Levine, S. B., Abbruzzese, E., & Mason, J. W. (2022). Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults. *Journal of sex & marital therapy*, 1–22. Advance online publication. https://doi.org/10.1080/0092623X.2022.2046221).

Differences between the gender transition industry's approach to gender dysphoria and the treatment of other medical conditions include not only the poor quality of evidence regarding safety and efficacy, but also attempts to silence standard scientific discussion and consideration of alternative hypotheses, failures to acknowledge existing data showing persistence of suicidality after intervening, the intentional impairment and destruction of normally formed and functioning male and female sexual organs to address psychological-psychiatric distress, the manipulation of language from standard medical definitions to accommodate novel ideology, and widespread failures in properly reporting research data related to gender transitioning. Each of these differences are discussed in detail in my declaration with appropriate examples and relevant scientific and professional citations.

When considering clinical practice guidelines, it is essential that physicians recognize the relative risks and benefits of such documents. If done properly, they can distill large data sets into actionable clinical recommendations. However, there is a long history of clinical practice guidelines that have later been found to be deficient, resulting in wasted medical resources, failure to achieve desired benefits, or to have caused substantial harm to patients. (See, e.g., Woolf, S. H., Grol, R., Hutchinson, A., Eccles, M., & Grimshaw, J. (1999). Clinical guidelines:

potential benefits, limitations, and harms of clinical guidelines. *BMJ (Clinical research ed.)*, 318(7182), 527–530. https://doi.org/10.1136/bmj.318.7182.527)

14. It is highly misleading to imply that the current Endocrine Society guidelines, first published in 2009 and revised in 2017 represent the opinions of the Societies 18,000 members. (Hembree, W. C., Cohen-Kettenis, P., Delemarre-van de Waal, H. A., Gooren, L. J., Meyer, W. J., 3rd, Spack, N. P., Tangpricha, V., Montori, V. M., & Endocrine Society (2009). Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*, *94*(9), 3132–3154. https://doi.org/10.1210/jc.2009-0345; Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., Hannema, S. E., Meyer, W. J., Murad, M. H., Rosenthal, S. M., Safer, J. D., Tangpricha, V., & T'Sjoen, G. G. (2017). Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism*, *102*(11), 3869–3903. https://doi.org/10.1210/jc.2017-01658). The committee that drafted these guidelines was composed of *less than a dozen* self-selected members. The guidelines were never submitted to the entire membership for comment and approval prior to publication. They also did not undergo external review. Such political methodologies are common in association "statements" and "endorsement" and not at all scientific nor reliable nor valid.

15. The hazard of making treatment recommendations based on studies with major methodological weaknesses can be readily seen by considering representative studies used by advocates of medical gender affirmation to justify this approach.

15A. For example, the study by De Vries and colleagues (de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;8(8):2276-2283) is often cited to support

longitudinal evidence of benefit from pubertal blockade. Although improvements in mood improved and the risk of behavioral disorders with pubertal blockade were found over baseline, in this study there was no control group. Thus, the authors were unable to determine the basis of this improvement. The authors acknowledge that psychological support or other reasons may have contributed to (or wholly caused) this observation. It is also important to note that gender dysphoria itself *did not diminish* in study subjects, and there were *no changes* in body image-related distress.

15B. The study by Turban and colleagues (Turban, J. L., King, D., Carswell, J. M., & Keuroghlian, A. S. (2020). Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*, *145*(2), e20191725) is often cited as proof that pubertal blockade prevents suicide in transgender youth. However, this study used an unreliable, biased sampling methodology. As stated in the paper, the authors considered "a cross-sectional online survey of 20,619 transgender adults aged 18 to 36 years" from the 2015 U.S Transgender Survey. This was an online survey of transgender and "genderqueer" adults recruited from trans-friendly websites. Among the many problems with this sampling methodology, there is NO evidence of study subject identities, NO way to assess for potential false subjects, and NO medical diagnosis for entry. No causation can be determined from this retrospective, cross-sectional design. Furthermore, the study failed to even assess Desisters and Regretters. Turban claimed that desisters and regretters would "not be likely" in this study group, which also only included adults. Thus, the study "does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender." Turban's misleading claim of lower suicidal ideation for treated patients excluded the most seriously mentally ill patients that would have been DENIED affirmation treatment. Those who received treatment with pubertal suppression, when compared

with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2– 0.6). In Table 3 of the paper, under "Suicidality (past 12 months)" reductions for suppressed group v non-suppressed were seen for ideation (50.6% v 64.8%) and "ideation with plan" (55.6% v 58.2%). However, it is important to note that suicidal "ideation with plan and suicide attempt" for the suppressed group INCREASED after treatment to 24.4% v 21.5% for the "non-treatment group." The most clinically significant result in this study — that "Affirmation Treatments INCREASED SERIOUS SUICIDE ATTEMPTS — was IGNORED BY THE AUTHORS (i.e., not statistically significant but clinically significant) = "Suicide attempts resulting in inpatient care" = 45.5% for suppression groups vs 22.8% for those who did not receive pubertal suppression. It would be most reasonable to conclude from an observation of 45% attempted suicide in the treated arm that the intervention was unsuccessful in improving health. Turban et al. ignored their own finding that a history of puberty suppression was associated with an INCREASE in recent serious suicide attempts. In sum, the Turban 2020 Pediatrics study, based on an unverified US Transgender Online Survey, tells us little about the effects of puberty suppression on children with gender dysphoria. (See, Michael Biggs, Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria. Archives of Sexual Behavior, accepted 14 May 2020, DOI: 10.1007/s10508-020-01743-6 and the multiple Letters to the Editor that criticized the multiple methodological errors in this study, https://pediatrics.aappublications.org/content/145/2/e20191725/tab-e-letters#re-pubertal-suppression-for-transgender-youth-and-risk-of-suicidal-ideation)

15C. The 2021 study of Bustos, et al., (Bustos, V. P., Bustos, S. S., Mascaro, A., Del Corral, G., Forte, A. J., Ciudad, P., Kim, E. A., Langstein, H. N., & Manrique, O. J. (2021). Regret

after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence. *Plastic and reconstructive surgery. Global open*, *9*(3), e3477) attempts to provide a systematic review of 27 observational or interventional studies that report on regret or detransition following gender-transition surgeries. A total of 7928 subjects were included in their meta analysis. The authors concluded that only 1% or less of those who had gender-transition surgeries expressed regret. It is important to understand the serious methodological limitations and high risk of bias contained within the analysis in the 2021 Bustos et al. study (see Expósito-Campos, P., & D'Angelo, R. (2021). Letter to the Editor: Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence. *Plastic and reconstructive surgery. Global open*, *9*(11), e3951). This includes failure to include major relevant studies addressing this question (e.g. Dhejne, C., Öberg, K., Arver, S., & Landén, M. (2014). An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Archives of sexual behavior*, *43*(8), 1535–1545), inaccurate analysis within one of the studies considered **(**Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018; 15: 582–590) and the general lack of controlled studies, incomplete and generally short-term follow-up, large numbers of lost subjects, and lack of valid assessment measures in the published literature addressing this question. As noted by Expósito-Campos and D'Angelo (2021), moderate to high risk of bias was present in 23 of the 27 studies included in the analysis. Furthermore, 97% of subjects analyzed were found within studies deemed to be of fair to poor scientific quality. Thus, this study cannot be used as strong support for the contention that regret is rare.

15D. The 2018 paper by Wiepjies, et al. (Wiepjes, C. M., Nota, N. M., de Blok, C., Klaver, M., de Vries, A., Wensing-Kruger, S. A., de Jongh, R. T., Bouman, M. B., Steensma, T.

D., Cohen-Kettenis, P., Gooren, L., Kreukels, B., & den Heijer, M. (2018). The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. *The journal of sexual medicine*, *15*(4), 582–590) is a retrospective review of records from all patients of the Center of Expertise on Gender Dysphoria gender clinic in Amsterdam from 1972-2015. While the study appears to report on the regret rates among a large cohort of adolescents (812) and children (548), regret is only reported for children and adolescents who had undergone gonadectomy once over 18 years of age. Of the adolescents, 41% started puberty suppression. Of those who started GnRH agonists, only 2% stopped this intervention (meaning that 98% of those who started puberty suppression progressed to cross-sex hormone therapy). An additional 32%, having already completed puberty, started cross-sex hormone therapy without use of a GnRH agonist. Classification of regret was very stringent, requiring physician documentation of patient verbalized regret after gonadectomy and start of sex-concordant hormones to treat the iatrogenic hypogonadism. This means there are significant limitations to the conclusions that can be drawn from 2018 paper by Wiepjies, et al. There is no discussion in this paper regarding adolescent regret of use of puberty blockers, cross-sex hormones or mastectomies. Importantly 36% of patients were lost to follow up. This is notable given that gonadectomy iatrogenically induces the pathologic state of primary hypogonadism. Affected patients have a lifelong dependency for exogenously administered sex-steroid hormones, and thus an acute need for ongoing follow-up. The number of lost subjects who experienced regret or completed suicides is unknown. It is also significant that the average time to regret was 130 months. The authors themselves acknowledge that it may be too early to predict regret in patients who started hormone therapy in the past 10 years.

15E. The 2021 study by Narayan et al (Narayan, S. K., Hontscharuk, R., Danker, S., Guerriero, J., Carter, A., Blasdel, G., Bluebond-Langner, R., Ettner, R., Radix, A., Schechter, L., & Berli, J. U. (2021). Guiding the conversation-types of regret after gender-affirming surgery and their associated etiologies. *Annals of translational medicine*, *9*(7), 605) examines anonymous survey results from 154 surgeons affiliated with WPATH. The response rate for this survey was 30%. Of the respondents, 57% had encountered patients with surgical regret. It is important to recognize that this study was specifically directed toward patients who had undergone surgical transition. Acknowledged biases of this study include selection bias, recall bias, and response bias. This type of study cannot accurately identify the prevalence in the transgender population as a whole, and is particularly limited in the ability to assess potential for regret in the pediatric population.

15F. The 2018 Olson-Kennedy paper (Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr.* 2018;172(5):431–436) presents the results of a survey of biologically female patients with male gender identity at the lead author's institution using a novel rating system for "chest dysphoria" created by the study authors. There were an equal number (68) of nonsurgical and post-surgical subjects surveyed. Those who had undergone bilateral mastectomies were reported to have less chest dysphoria than those who did not receive this intervention. Limitations of this study include convenience sampling of nonsurgical study subjects with high potential for selection bias, cross-sectional design, and lack of validation of the primary outcome measure. Test validation is particularly relevant in assessing adolescent questionnaires due to a variety of cognitive and situational

factors in this population (see Brener, N.D., J. Billy, and W.R. Grady. 2003. "Assessment of Factors Affecting the Validity of Self-Reported Health-Risk Behavior among Adolescents: Evidence from the Scientific Literature." *Journal of Adolescent Health* 33 (6): 436–57). Rigorous validation methods have been previously used in several other established questionnaires addressing adolescent self-perception (see Palenzuela-Luis, N., Duarte-Clíments, G., Gómez-Salgado, J., Rodríguez-Gómez, J. Á., & Sánchez-Gómez, M. B. (2022). Questionnaires Assessing Adolescents' Self-Concept, Self-Perception, Physical Activity and Lifestyle: A Systematic Review. *Children (Basel, Switzerland)*, *9*(1), 91). As previously noted, this study cannot provide information about a causal relationship between the intervention and outcome observed.

15G. The 2021 Almazan study (Almazan, A.N. & A.S. Keuroghlian. (2021). Association Between Gender-Affirming Surgeries and Mental Health Outcomes. *JAMA Surgery, 156*(7): 611–618) attempts to address mental health outcomes in relation to gender-transition surgery. As previously noted, this study relies upon data from the 2015 US Transgender Survey. Limitations and weaknesses of this survey tool includes convenience sampling, recruitment of patients through transgender advocacy organizations, demand bias (a.k.a. the good subject effect), a high number of respondents who reported having not transitioned medically or surgically (and reported no desire to do so in the future), and several data irregularities. One notable data irregularity was that a high number of respondents reported that their age was exactly 18 years. As noted by D'Angelo and colleagues, these irregularities raise serious questions about the reliability of the USTS data (D'Angelo, R., et al. (2021). One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Archives of sexual behavior*, *50*(1): 7–16. https://doi.org/10.1007/s10508-020-01844-2), and therefore, the reliability of conclusions based on that data.

15H. In his declaration, Dr. Rosenthal cites the 2021 paper by Green et al (Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *J Adolescent Health* 1-7 (2021) to support his assertion that gender affirming therapy lowers depression and suicide. Similar to the major methodological weaknesses noted above, this study relied upon a non-probability convenience sample of youth who identified as LGBTQ. Recruitment was made by targeted ads on Facebook, Twitter and Snapchat. In addition to the inherent bias of such study methodology, the data obtained by cross-sectional analysis cannot determine whether there is a causal relationship between access to gender affirming medical interventions and changes in depression or suicide.

15I. Rosenthal's citation of the paper by Turban et al (Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE 17(1) 2021; https://doi.org/10.1371/journal. pone.0261039) is similarly misleading as this study relied upon data from the same 2015 US transgender survey for which the major methodological weaknesses were discussed in detail above (¶15B)

16. There are major and highly significant differences between male and female responses to many drugs including sex hormones. (See, e.g., Madla, C. M., Gavins, F., Merchant, H. A., Orlu, M., Murdan, S., & Basit, A. W. (2021). Let's talk about sex: Differences in drug therapy in males and females. *Advanced drug delivery reviews*, 113804. Advance online publication. https://doi.org/10.1016/j.addr.2021.05.014). Giving estrogen to a biological male is not equivalent to giving the same hormone to a biological female. Likewise, giving testosterone to a biological female is not equivalent to giving the same hormone to a biological male. (See for example Soldin, O. P., & Mattison, D. R. (2009). Sex differences in pharmacokinetics and pharmacodynamics. Clinical pharmacokinetics, 48(3), 143–157 and Pogun S., Yararbas G. (2010) Sex

Differences in Drug Effects. In: Stolerman I.P. (eds) Encyclopedia of Psychopharmacology. Springer, Berlin, Heidelberg.). Differences are not limited to pharacokinetic effects but are present even at the cellular level. (See, e.g., Walker, C. J., Schroeder, M. E., Aguado, B. A., Anseth, K. S., & Leinwand, L. A. (2021). Matters of the heart: Cellular sex differences. *Journal of molecular and cellular cardiology*, S0022-2828(21)00087-0. Advance online publication. https://doi.org/10.1016/j.yjmcc.2021.04.010). Failure to acknowledge these differences can have tragic consequences. For example, in addition to the inherent sterilizing effect of cross-sex hormone administration, non-physiological levels of estrogen in males has been shown to increase the risk of thromboembolic stroke above the incidence observed in females (e.g. Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., Hunkeler, E., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D., Silverberg, M. J., Safer, J., Slovis, J., Tangpricha, V., & Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. *Annals of internal medicine*, *169*(4), 205–213. https://doi.org/10.7326/M17-2785).

17. The claim that adolescents with persistent gender dysphoria after reaching Tanner Stage 2 *almost always* persist in their gender identity in the long-term whether or not they were provided gender affirming care is not supported by high quality scientific evidence. Frequent citation of a book chapter by Turban, De Vries and Zucker does not provide evidence in support of this claim. Within the chapter cited it states, "The natural history of gender identity for children who express gender nonconforming or transgender identities is an *area of active research.*" Only a single reference is found, and this is itself another book (Cohen-Kettenis PT, Pfäfflin F: Transgenderism and Intersexuality in Childhood and Adolescence: Making Choices.

London, Sage, 2003). Within the text of the Cohen-Kettenis book, *there is no experimental evidence to support the assertion that nearly all Tanner stage adolescents have persistent transgendered identity*. In fact, *in Chapter 4 of this text, evidence is presented that the majority of evaluated subjects did not have persistence* but rather eventually presented as homosexual adults. Cited references for this outcome include: Green, R. (1987). The "sissy boy syndrome" and the development of homosexuality. New Haven, CT: Yale University Press.; Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. Journal of Pediatric Psychology,4, 29-41.; Zucker, K. J., & Bradley, S. J. (1995). Gender identity disorder and psychosexual problems in children and adolescents. New York/London: Guilford Press.; Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. Journal of Nervous and Mental Disease, 172, 90-97.

18. Serious Methodological Limitations, Flaws, and Defects in the Gender Transition Industry's Methods for the Diagnostic-Labelling of "Gender Dysphoria": The DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) involves an often controversial consensus seeking, (not scientific evidence seeking), political-voting process that began historically as an attempt to construct a reliable dictionary for psychiatry. The DSM has historically included unreliable, since debunked, diagnoses such as "multiple personality disorder" that fueled a harmful "craze" damaging vulnerable patients until scientists, legal professionals, juries, and licensing boards put a stop to it. (See the detailed discussion below). It is important for legal professionals to understand that the DSM was created using a consensual, political process of committees and voting and does not depend upon an evidence-based, uniformly valid and reliable scientific process. Small groups of professionals, often with ideological agendas, can form

committees and create "diagnoses" to be "voted" into the DSM. Much of DSM content is decided by the "voting" of small committees of advocates and activist practitioners whose judgment may suffer from significant financial conflicts of interest — as appears to be the case with all three of the plaintiffs' experts in this case.

19. Well-Documented Methodological Limitations, Flaws, and Defects in Gender Identity ("Transgender") Subjective Clinical Assessments: The clinical assessment methodology in sex discordant gender medicine is currently limited to self-report information from patients without objective scientific markers, medical tests, or scientific assessment tools. There are no reliable radiological, genetic, physical, hormonal, or biomarker tests that can establish gender identity or reliably predict treatment outcomes. A few hours of conversation with often poorly trained social workers often provides the only gatekeeping process to severe and irreversible iatrogenic surgical and hormonal injuries. Most importantly, *the long-term effects of "transitioning" have never been scientifically validated*. No valid-reliable methodology for such assessments has been accepted by the relevant scientific community and it appears that no known error rates for such assessments have ever been published. A more detailed discussion of the foundational science documenting the limitations and methodological defects in this field is offered below.

20. Essential Methodological Problems in the Gender Transition Industry: The research is characterized by sampling errors, the misreporting of findings, the misreporting of relevant history, misquoting of research studies, low quality research designs, failures to complete randomized clinical trials, and widespread confirmation bias, including the failure to properly explore alternative hypotheses (e.g., social contagion, mental illness, complex developmental processes, family dynamics, etc.), and other failures of basic scientific methodology. It is essential to properly consider alternative theories/hypotheses for the rapid and nearly exponential increase

of transgender cases—such as social contagion, mental illness, and/or complex developmental processes—especially as reportedly driven by news media, social media "YouTube "influencers" (who reportedly sell "transitioning" to vulnerable youth on social media), educational systems (that reportedly pressure 1st graders to "identify as non-binary"), as well as political-activist "pro-transition" health care workers (too few of whom seem to have carefully reviewed and understood the relevant scientific history and ongoing controversies in this field).

21. TERMINOLOGY - BIOLOGICAL SEX: Biological sex is a term that specifically refers to a member of a species in relation to the member's capacity to either donate (male) or receive (female) genetic material for the purpose of reproduction. Sex thus cannot be "assigned at birth" because it is permanently determined by biology at conception. This remains the standard definition that has been accepted by the relevant scientific community and used worldwide by scientists, medical personnel, and society in general for decades. The scientific and clinical measurement of sex is done with highly reliable and valid objective methodologies. Visual medical examination of the appearance of the external genitalia is the primary methodology used by clinicians to recognize sex. In cases where genital ambiguity is present, additional testing modalities including chromosomal analysis, measurement of hormone levels, radiographic imaging of internal sexual anatomy and biological response to provocative testing are utilized. The measurement and assessment of biological sex has been documented by valid-reliable research published in credible journals, and is accepted by the relevant scientific community. The error rate for the measurement and assessment of biological sex is very low, below 1%.

22. TERMINOLOGY - GENDER: Gender, a term that had traditionally been reserved for grammatical purposes, is currently used to describe the psychological and cultural characteristics of a person in relation to biological sex. Gender in such new definitions would therefore

exist only in reference to subjective personal perceptions and feelings and societal expectations, but not biology. The term "gender" is currently used in a variety of ways and has thus become a controversial and unreliable term that means different things to different observers often varying according to political and ideological positions. The only definition of gender accepted by the worldwide, relevant scientific (biology, genetics, neonatology, zoology, medicine, etc.) community retains the historic biological connection to reproductive purpose with other definitions mired in controversy. The reliability and validity of various usages of the term "gender" is currently quite controversial and the relevant scientific community has accepted no use other than in relation to biological sex, which includes participate in activities related to reproduction. The serious dangers of incorrectly using the term "gender" is acknowledged by the Endocrine Society (Bhargava, A., Arnold, A. P., Bangasser, D. A., Denton, K. M., Gupta, A., Hilliard Krause, L. M., Mayer, E. A., McCarthy, M., Miller, W. L., Raznahan, A., & Verma, R. (2021) Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement. *Endocrine reviews*, bnaa034. Advance online publication. https://doi.org/10.1210/endrev/bnaa034). In addition, the error rate for multiple uses of the term "gender" outside of the accepted biologically related use is unknown, untested, and unpublished. The measurement and assessment of biological sex and gender has been documented by valid-reliable research published in credible journals, and is accepted by the relevant scientific community. The error rate for the measurement and assessment of biological sex and gender is very low, below 1%.

23. TERMINOLOGY - GENDER IDENTITY: Gender identity refers to a person's individual experience and perception and unverified verbal patient reports of how they experience being male or female or a combination of these or other categories. The term "gender identity" is

currently controversial. It is a term that means very different things to different observers often varying according to political, ideological, religious, and other factors. There is no current worldwide definition of "gender identity" accepted by the relevant scientific (cf. clinical) community. The reliability and validity of the term "gender identity" is controversial and not accepted by the relevant scientific community. The measurement error rate for non-biological "gender identity" is unknown, untested, and unpublished and could be very high.

24. TERMINOLOGY - SEXUAL ORIENTATION: Sexual orientation refers to a person's enduring pattern of arousal and desire for intimacy with males, females, or both.

25. TERMINOLOGY - DNA and CHROMOSOMES: Sex is genetically encoded at the moment of conception due to the presence of specific DNA sequences (i.e. genes) that direct the production of signals that influence the formation of the bipotential gonad to develop into either a testis or ovary. This genetic information is normally present on X and Y chromosomes. Chromosomal sex refers to the normal complement of X and Y chromosomes (i.e. normal human males have one X and one Y chromosome whereas normal human females have two X chromosomes). Genetic signals are mediated through the activation or deactivation of other genes and through programmed signaling of hormones and cellular transcription factors. The default pattern of development in the absence of external signaling is female. The development of the male appearance (phenotype) depends upon active signaling processes.

26. BIOLOGICAL SEX IS BINARY—NOT A CONTINUUM—FOR 99%+ of MAMMALS INCLUDING HUMANS: For members of the human species (and virtually all mammals), sex is normatively aligned in a binary fashion (i.e., either male or female) in relation to biologic purpose. The presence of individuals with disorders of sexual development (along the

range of the established Prader scale) does not alter this fundamental reality. Medical recognition of an individual as male or female is correctly made at birth in nearly 99.98% of cases according to external phenotypic expression of primary sexual traits (i.e., the presence of a penis for males and presence of labia and vagina for females). The recognition of an individual as male or female made at birth according to biological features has been documented by valid-reliable research published in credible journals, and is generally accepted by the relevant scientific community. The error rate for the measurement and assessment of an individual as male or female made at birth according to biological features is very low indeed, certainly below 1%.

27. THE GENITAL-BIOLOGICAL FUNCTION OF REPRODUCTION: Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e. reproduction). Internal structures (e.g. gonad, uterus, vas deferens) normatively align in more than 99.9%+ of mammals with external genitalia, including humans. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, neonatology, developmental biology, genetics, and other relevant fields. In my opinion, all relevant sciences agree that the development of genital structures is intrinsically oriented to biological reproduction.

28. BIOLOGICAL ASSESSMENT OF SEX: Reliance upon external phenotypic expression of primary sexual traits is a highly accurate, reliable and valid means to assign biologic sex. In over 99.9% of cases, this designation will correlate with internal sexual traits and capacity for normal biologic sexual function. Sex is therefore not "assigned at birth" but is rather recognized at birth. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, psychiatry, neonatology, biology, genetics, gynecology, and other fields.

29. DISORDERS OF SEXUAL DEVELOPMENT ARE VERY RARE: Due to the complexity of the biological processes that are involved in normal sexual development, it is not surprising that a very small number of individuals are born with defects in this process (1 in 5,000 births). Defects can occur through either inherited or de *novo* mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia. Such detection measurements are reliable and valid and accepted by the relevant scientific community. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, neonatology, gynecology, psychiatry, biology, genetics, and other fields. See Leonard Sax (2002) How common is lntersex? A response to Anne Fausto-Sterling, The Journal of Sex Research, 39:3, 174-178, DOI: 10.1080/00224490209552139

DISORDERS OF SEXUAL DEVELOPMENT ARE NOT A THIRD SEX: Normal variation in external genital appearance (e.g. phallic size) does not alter the basic biologic nature of sex as a binary trait. "Intersex" conditions represent disorders of normal development, not a third sex. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

30. DISORDERS OF SEXUAL DEVELOPMENT REQUIRE ASSESSMENTS OF OBJECTIVE EVIDENCE: The medical care of persons with disorders of sexual development (DSDs) is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to other diseases, diagnostic tools such as the Prader scale are used to assess, measure, and assign a "stage" to the severity of the deviation from normal

(e.g. assessments of objective, reliable evidence). In children with DSDs, characterization based upon phenotype alone does not reliably predict chromosomal sex nor does it necessarily correlate with potential for biological sexual function. Decisions on initial sex assignment in these very rare cases require detailed assessment of objective, reliable medical evidence by a team of expert medical providers. In my opinion, this view is generally accepted by the relevant scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

31. INTERSEX CONDITIONS REQUIRE PROPER CONSIDERATION OF ALTERNATIVE HYPOTHESES AND TREATMENT PLANS: Standard medical practice in the treatment of persons with DSDs has evolved with growing understanding of the physical, psychological, and psychiatric needs and outcomes for affected individuals. Previously, it was felt that a definitive sex assignment was necessary shortly after birth with the belief that this would allow patients with a disorder of sexual development to best conform to the assigned sex and so parents-caregivers could help socialize the child to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a reliable prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include chromosomal sex, phenotypic appearance of the external genitalia, and parental desires. The availability of new information can, in rare circumstances, lead to sex reassignment. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent. See Lee, P. A. et al. Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr 85, 158-180, doi:10.1159/000442975 (2016)). In my opinion, this view is generally accepted by the relevant

scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

32. METHODOLOGICAL DEFECTS of the GENDER TRANSTION INDUSTRY - WHY IS THE TRANSGENDER MEDICINE FIELD STILL SO CONTROVERSIAL AFTER DECADES OF RESEARCH?:

- Despite several highly defective research efforts, the gender transition industry has failed to prove long term benefits that outweigh the reported harms, dangers, and serious injuries of "gender affirmation" interventions—including inability to reach orgasm, vaginal atrophy, compromised cognitive function, lifelong reliance on medication and repeated surgical intervention to deal with the cumulative effects of these iatrogenic harms, stunted growth, damage to social support systems, and increased risk of serious suicide attempts.
- The gender transition industry has repeatedly presented false, deceptive, and misleading information to the public and to patients regarding the known risks, dangers, injuries and benefits of "affirmation treatments." (E.g. the Bränström, Turban, and related research errors of omission and misreporting.)
- The Gender Transition Industry has failed to generate reliable and valid treatment outcome research sufficient to support this risky medical experiment. (E.g., the national reviews of England (NICE), Sweden, Finland, Cochrane review, etc).
- Because of the lack of competent, valid, peer reviewed published research support, the gender transition industry relies upon support from "professional associations." Yet such associations are engaged in consensus-seeking-political voting methodologies and not evidence-based, peer reviewed science. Such political-

professional associations have made similar, disastrous mistakes in the past. For example, the American Medical Association supported racist, "junk" science eugenics "treatments" in the 1930s and the American Psychiatric Association did not act to prevent or halt the harms of the repressed-memory/multiple personality industry of the 1990s.

33. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY INCLUDE LIMITATIONS and HAZARDS OF RELYING ON UNVERIFIED PATIENT SELF-REPORT DATA WITH NO OBJECTIVE EVIDENCE: In contrast to disorders of sexual development, gender dysphoria cannot be reliably, objectively assessed, as it is based on patient self-reports. (There are no blood tests, no x-rays, no lab results, and no objective data.) Individuals who verbally report experiencing significant distress due to perceived discordance between gender identity and sex cannot currently be reliably, validly, and objectively assessed as experiencing "gender dysphoria." (See American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th edn, (2013).) Although gender perceptions, feelings, and "identity" usually align with biological sex, some individuals report experiencing discordance in these distinct traits. Specifically, for example, biologic females may report experiencing that they identify as males and biologic males may report experiencing that they identify as females. As gender by definition is distinct from biological sex, one's gender identity does not change a person's biological sex. There is currently no known reliable and valid methodology for assessing the accuracy or nature of unverified, verbal reports of discordant "identity." There is thus no known "error rate" for relying upon such reports to engage in hormonal and surgical treatments that might result in lasting, irreversible damages to normal, healthy organs and the destruction of normal biological functions (e.g. sterility), as the current research documents. In my opinion, this

view is generally accepted by the relevant scientific communities in endocrinology, urology, surgery, neonatology, gynecology, psychiatry, biology, genetics, and other fields.

34. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY include the KNOWN LIMITATIONS OF RELYING ON UNVERIFIED, PATIENT SELF-REPORT DATA UNRELIABLY ASSESSED BY HEALTH CARE PROFESSIONALS. The relevant science documents that mental health care professionals are unreliable human "lie detectors" ("often no better than flipping a coin"). Currently, there is no known methodology for reliably discerning true from false patient reports without corroborating evidence such as radiology, lab tests, or other objective evidence. The gender transition industry's sole reliance upon patient self-report data carries unknown risks of errors, misinformation, deception and lasting harm to patients from treatments that deliberately damage healthy organs and destroy essential normal bodily processes (e.g. often causing sterility). Assessment of gender dysphoria currently depends almost entirely upon unverified, self-reported evidence provided by patients. A patient's spoken or written reports of alleged "memories" of symptoms and behaviors are the only source of evidence for the diagnosis in many cases. This is a source of potentially profound unreliability in patient care as the relevant science documents that physicians are poor "lie detectors"—often no more reliable in discerning false reports than flipping a coin—and sometimes much worse. The relevant research also documents that even though humans (including therapists) are poor "lie detectors," many poorly trained physicians and mental health professionals personally—and falsely—believe they are "experts" at this complex and difficult task. See, e.g., Vrij, Aldert, Granhag, P. and Porter, S. (2010) Pitfalls and opportunities in nonverbal and verbal lie detection. Psychological Science In The Public Interest, 11 (3). pp. 89-121. ISSN 1529-1006 10.1177/1529100610390861. The final error that I will highlight is that professional lie catchers

tend to overestimate their ability to detect deceit. Research has consistently shown that when professional lie catchers and laypersons are compared, "professionals are more confident in their veracity judgments but are NO more accurate" (emphasis added). See also Rosen, G. M. and Phillips, W.R., A Cautionary Lesson from Simulated Patients, *Journal of the American Academy of Psychiatry and Law*, 32, 132-133, (2004).

35. METHODOLOGICAL DEFECTS of the GENDER TRANSITION INDUSTRY include the reliance upon (often poorly trained) mental health professionals to assess unverified patient reports. Although much of medicine became science-based in the 20th century, the mental health field reportedly continues to lag behind.

The gender transition industry often involves social workers or other mental health professionals "assessing" patients reporting gender dysphoria to determine if they will "benefit" from "affirmation" medical interventions. Given the extraordinary lack of competent, methodologically sound research justifying the use of gender affirmation "treatments" (as demonstrated in independent reviews by England, Sweden, Finland, the Cochrane review, and others, see below), there is no method for mental health professionals to reliably determine who might "benefit" from experimental interventions. Such unreliable assessment protocols risk harm to patients as they depend upon the widespread, unreliable method of having psychotherapists depend upon "clinical judgment" methodologies to make life-changing decisions and offer "professional" opinions with little or no scientific validity. See, e.g., Mischel, W. Connecting Clinical Practice to Scientific Progress, Psychological Science in the Public Interest, November 2008, vol 9, no 2 i-ii. The past President of the Association for Psychological Science, Prof. Walter Mischel,

stated "the current disconnect between psychological science and clinical practice is an unconscionable embarrassment." See Mischel, W. Connecting Clinical Practice to Scientific Progress, Psychological Science in the Public Interest, Vol 9, No 2, 2009.

Over the past century many components of the health care system—surgery, radiology, laboratory testing, internal medicine, pharmacological systems, etc.—became science-driven and far more effective and reliable. Courts are often unaware that this transformation—moving from widespread use of unreliable methodologies to the widespread use of reliable science-based methodologies—has, in many ways, not yet occurred in the mental health system. See, e.g., West, Catherine, 'An Unconscionable Embarrassment,' Association for Psychological Science, Observer, October 2009, see http://www.psychologicalscience.org/index.php/publications/observer/2009/october-09/an-unconscionable-embarrassment.html; See, also Baker, T., McFall, R. & Shoham, V., Current Status and Future Prospects of Clinical Psychology: Toward a Scientifically Principled Approach to Mental and Behavioral Health Care, Psychological Science in the Public Interest, Vol. 9, No. 2 (2009); see also Harrington, A., Mind Fixers: Psychiatry's Troubled Search for the Biology of Mental Illness, W. W. Norton & Company; 1st edition, April 16, 2019; see also Dawes, R.M., House of cards: Psychology and psychotherapy built on myth, New York: Free Press (1997); see also Garb, H. N., & Boyle, P. A (2003). Understanding why some (mental health) clinicians use pseudoscientific methods: Findings from research on clinical judgment. In S. O. Lilienfeld, S. J. Lynn, &. J. M. Lohr (Eds.), Science and pseudo-science in clinical psychology (pp. 17–38). New. York, NY: Guilford Press.

36. DYSPHORIC REPORTS ARE COMMON FROM CHILDREN WITH A RANGE OF ILLNESSES: Reports of feelings of anxiety, depression, isolation, frustration, and embarrassment are not unique to children with gender dysphoria, but rather are common to children

who differ physically or psychologically from their peers. Difficulties are accentuated as children progress through the normal stages of neuro-cognitive and social development. In my clinical practice of pediatric endocrinology, this is most commonly seen in children with diabetes. Attempts to deny or conceal the presence of disease rather than openly acknowledge and address specific needs can have devastating consequences including death. With proper acknowledgment of the similarity and differences between children with gender dysphoria and other developmental challenges, prior medical experience in treating a range of reported troubles can guide the development of effective approaches to both alleviate suffering and minimize harm to school aged and adolescent children experiencing gender dysphoria.

37. COURTS SHOULD BE AWARE THAT CLINICAL EXPERIENCE IN THE MENTAL HEALTH FIELDS—WHERE CLINICIANS OFTEN LACK ACCURATE FEEDBACK—IS OFTEN OF LIMITED VALUE: As the gender transition industry routinely permits poorly qualified social workers or other mental health professionals to subjectively make life changing decisions in gender dysphoria cases—such mental health professionals often unreliably overestimate their ability to offer such "crystal ball" assessments and predictions. Few of these professionals seem aware of the research showing the grave limitations on the experience, judgment, and methodologies of mental health professionals. See, e.g., Tracey, T.J., Wampold, B.E., Lichtenberg, J.W., Goodyear, R. K., (2014) Expertise in Psychotherapy: An Elusive Goal, American Psychologist, Vol. 69, No. 3, 218-229. "In a review of expertise across professions, Shanteau, J. (1992). [Competence in experts: The role of task characteristics. *Organizational Behavior and Human Decision Processes, 53*(2), 252–266.] identified several professions in which practitioners develop expertise, which he defined as increased quality of performance that is gained with additional experience. These professions, which demonstrate there can be a relation

between experience and skill, include astronomers, test pilots, chess masters, mathematicians, accountants, and insurance analysts. Shanteau also identified several professions for which experiential expertise was not demonstrated, including [mental health professionals]. He attributed the differences between the two types of professions to the *predictability of their outcomes and the unavailability of quality feedback*." For example, airline pilots, or even more clearly Navy fighter pilots who land on aircraft carriers practice their professions in full view of hundreds of people. If they err, people die. If they are, off course, unstable, or inaccurate in their performance, immediate consequences, retraining or loss of profession is the immediate outcome. In contrast, a social worker, psychologist, or psychiatrist, sitting alone in a room with a troubled patient can make erroneous statements, use unreliable methodologies (e.g., naively believing whatever patients tell them or believing that they are "professional human lie detectors"), believe false and misleading notions about human memory, demonstrate ignorance of the serious defects in transgender treatment research, and fail to properly inform patients of the risks and benefits of treatments, etc. Mental health professionals can make such egregious errors for decades without receiving timely, accurate feedback. Without accurate feedback there is a failure of the learning process and improvements are difficult or not possible. Such limiting processes can continue for many years of practice. This is why mental health professions have been listed as doing the type of work that often does not lead to improvements in "clinical experience"—even over many years of practice. Gender discordant ("transgender") patients are rarely, if ever, informed of these limitations on mental health professionals' knowledge, training, or experience nor the limitations of mental health "assessments" based on unverified self-reported "memory" data.

38. The World Professional Association for Transgender Health (WPATH), the American Academy of Pediatrics (AAP), and the Endocrine Society: This methodological critique and

history of association errors and misadventures is quite informative when assessing the "professional association" consensus seeking methodologies including voting and political activities such as those of WPATH, the AAP, the American Endocrine Society and similar groups as they adopt support for the "politically correct" but scientifically defective, ideologically driven gender transition industry. Consensus seeking (voting) methods are not scientific evidence-based methodologies. Courts should take care not to be deceived by the "positions" of Associations—no matter how large or vocal. The net effect of many the gender transition industry's methods and procedures is the sterilization of tens of thousands of children, adolescents, and adults. This is a sobering reminder of previous, now infamous, medical misadventures. (See Hruz, PW, Mayer, LS, and McHugh, PR, "Growing Pains: Problems with Puberty Suppression in Treating Gender Dysphoria," The New Atlantis, Number 52, Spring 2017 pp. 3 -36; See also McHugh, P., Psychiatric Misadventures, The American Scholar, Vol. 62, No. 2 (Spring 1993), pp. 316-320).

39. The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM): A final example of the methodological limitations of relying upon "association voting" methods is the Diagnostic and Statistical Manual of the American Psychiatric Association. The DSM (and also the International Classification of Diseases- ICD) system(s) have confused some courts in the past. Simply put, reliability data, validity methodological analyses, and error rates are not supplied nor supported by the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM).

The current American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (Version 5) employs the term "Gender Dysphoria" and defines it with separate sets of criteria for adolescents and adults on the one hand, and children on the other. It is important to appreciate the DSM for what it is and what it is not. The DSM began as an attempt to create a

dictionary for psychiatry. The process by which DSM classifications are created involves voting by committee—this is not a reliable-valid scientific process. The committees' recommendations are approved or rejected by superordinate committees. DSM content is largely decided by consensus-seeking methodologies—such as "voting" by small committees of (sometimes) advocates and activist practitioners whose judgment may suffer from significant financial conflicts of interest. The limitations of the DSM methodology are well known in the relevant scientific community. In my opinion, these views are generally accepted by the relevant scientific community.

In sum, professional association "positions" are not based upon competent, credible, reliable and valid scientific methodologies. Professional association "positions" on gender affirmation assessments and treatments remain very socially, medically, and scientifically controversial—and increasingly so. The association "positions"—since they are produced by voting and not methodologically reliable-valid evidence—have not been generally accepted by the relevant scientific community and they have no known, nor published, error rates.

40. PATIENTS' RIGHTS TO TESTED, PROVEN TREATMENTS and INFORMED CONSENT HAVE BEEN VIOLATED IN THE PAST BY ETHICAL FAILURES IN THE MEDICAL and MENTAL HEALTH SYSTEMS. Using experimental procedures on uninformed, vulnerable patients is unethical and improper. Some of the most tragic chapters in the history of medicine include violations of informed consent and improper experimentation on patients using methods and procedures that have not been tested and validated by methodologically sound science—such is the case with the gender transition industry. The history of the infamous Tuskegee studies, the Nazi and Imperial Japanese wartime experiments, lobotomies (e.g., Dr. Egas Moniz received the 1949 Nobel Prize in Medicine for inventing lobotomies as a "treatment" for schizophrenia. See https://www.nobelprize.org/prizes/medicine/1949/moniz/article/),

recovered memory therapy-multiple personality disorders, rebirthing therapy (see, e.g., Janofsky, M. Girl's Death Brings Ban on Kind of 'Therapy'. New York Times. April 18, 2001; see also Peggy Lowe, Rebirthing team convicted: Two therapists face mandatory terms of 16 to 48 years in jail, Rocky Mountain News, April 21, 2001), coercive holding therapy (see, Hyde, J. "Holding therapy appears finished, State orders the last practitioner of holding therapy to end controversial method" Deseret News, Feb 13, 2005), and other tragic examples should serve as a stark warning to medical providers to properly protect the rights of patients and their families to a proper informed consent process and to not be subjected to experimental, unproven interventions such as gender transition "treatments." It is now universally agreed that medical and psychotherapy patients have a right to proper informed consent. Professional ethics codes, licensing rules and regulations, hospital rules and regulations, state and federal laws, and biomedical conventions and declarations all protect patients' right to informed consent discussions of the risks and benefits of proposed treatments and alternative treatments including no treatment. See Jonson AR, Siegler M, Winslade, WJ: Clinical Ethics, New York: McGraw Hill, 1998, ("Informed consent is defined as the willing acceptance of a medical intervention by a patient after adequate disclosure by the physician of the nature of the intervention, its risks, and benefits, as well as of alternatives with their risks and benefits.") See also Katz, A., Webb, S., and Committee on Bioethics, Informed Consent in Decision-Making in Pediatric Practice, Pediatrics, August 2016, 138 (2) e20161485; DOI: https://doi.org/10.1542/peds.2016-1485 at https://pediatrics.aappublications.org/content/138/2/e20161485

Tragically, however, as I will discuss in detail below, we now have much evidence supporting increasing concerns that the true risks and benefits of Sex Discordant Gender

("transgender") transition "treatments" are NOT being properly and ethically presented to patients by providers (surgeons, endocrinologists, therapists, etc). Similarly, many of the published "pro-transition" research studies reviewed in this declaration have misrepresented to the public the actual risks and benefits of gender affirming medical interventions. The gender transition industry has produced research claiming evidence supporting the use of controversial "treatments" when, in fact, their own study data more likely support the alternative hypothesis that so-called "transition" intervention procedures might produce higher risks of anxiety and more serious suicide attempts requiring hospitalization**.** Expert witnesses in cases involving issues related to sex discordant gender transition interventions are duty bound and required by licensing rules to truthfully and fully disclose to courts and legal professionals the well-documented risks, international controversies, and published misrepresentations involving the still unproven gender transition methods and procedures.

42. ONE OF THE MOST SERIOUS OF ALL METHODOLOGICAL ERRORS, CONFIRMATION BIAS, PLAGUES THE RESEARCH OF THE GENDER TRANSITION INDUSTRY: Confirmation bias is one of the most serious and potentially dangerous errors in the assessment-diagnosis-treatment process of medicine. One of the key methodologies in science and in proper investigations-assessments of all kinds—including expert witness review and testimony—is the generation and testing of multiple alternative investigative hypotheses. From US Public Junior High Schools (typically first taught to 8th Graders) through competent M.A., M.S.W., and all Ph.D. and M.D. graduate programs, students and professionals at all levels are taught that the central methodology for science and for a proper assessment-diagnosis-treatment or expert witness report involves the generation and testing of alternative investigative hypotheses. Investigative hypotheses, once generated, should be rationally, properly, and fairly explored

to see if actual, factual evidence supports or refutes the hypotheses. A common and serious error in improper assessments-diagnoses-treatments is "confirmation bias," the failure to generate and then explore alternative hypotheses. With confirmation bias, the often poorly trained and/or biased physician, investigator, expert, or therapist applies a narrow "tunnel vision" process to support a single, favorite, biased, pre-conceived hypothesis in a case. (See Garb, H. N., & Boyle, P. A (2003). Understanding why some clinicians use pseudoscientific methods: Findings from research on clinical judgment. In S. O. Lilienfeld, S. J. Lynn, &. J. M. Lohr (Eds.), Science and pseudoscience in clinical psychology (pp. 17–38). New. York, NY: Guilford Press.; see also Plous, Scott (1993). The Psychology of Judgment and Decision Making. p. 233; Nickerson, Raymond S. (June 1998). "Confirmation Bias: A Ubiquitous Phenomenon in Many Guises". Review of General Psychology 2 (2): 175–220. doi:10.1037/1089-2680.2.2.17; Joshua Klayman and Young-Won Ha, Confirmation, Disconfirmation, and Information in Hypothesis Testing, Psychological Review, 1987, Vol.94, No. 2, 211-228.) Currently, too many gender transition industry providers appear to violate the requirement to properly generate, explore, and disclose alternative hypotheses for assessments/diagnoses and treatments. In my opinion such failures, including the demand that all alternative hypotheses and treatments be banned as forms of "conversion" therapy, risk institutionalizing confirmation bias —a dangerous form of negligent practice. See Smith, T. Summary of AMA Journal of Ethics article on cognitive biases, Four widespread cognitive biases and how doctors can overcome them (e.g., confirmation bias, anchoring bias, affect heuristic, and outcomes bias) at https://www.ama-assn.org/delivering-care/ethics/4-widespread-cognitive-biases-and-how-doctors-can-overcome-them. ("Physicians are human and, therefore, constantly vulnerable to cognitive bias. But this imperfection is not just theoretical. It can have huge effects on patient care.")

43. CONFIRMATION BIAS CAN PREVENT COMPLEX, COMPREHENSIVE DIAGNOSIS AND TREATMENT EXPLORING ALTERNATIVE HYPOTHESES: By demanding the immediate and un-investigated "affirmation" of a sex discordant gender identity patient's requests for so-called "transitioning"—without conducting a detailed, proper, medical assessment of alternative hypotheses—the gender transition industry is attempting to enforce and institutionalize the methodological failure of "confirmation bias." By disparaging as "conversion therapy" all forms of psychotherapy, coping-and-resilience training, cognitive behavioral therapy for depression/anxiety, the gender transition industry is failing to treat individual patients according to the basic requirements and principles of competent medical assessment, diagnosis, and treatment. The current scientific evidence does not support the current treatments nor methods endorsed and aggressively marketed and demanded by the gender transition industry. Its general refusal to properly investigate or even consider alternative hypotheses, alternative diagnoses, and alternative treatments is, in my view, unethical misconduct. For example, many peer reviewed, properly conducted, published research reports demonstrate that cognitive-behavioral therapy is a very low-risk, safe, and highly effective treatment for depression and anxiety disorders. See, e.g., Mor N, Haran D. Cognitive-behavioral therapy for depression. J Psychiatry Relat Sci. 2009;46(4):269-73. PMID: 20635774, https://pubmed.ncbi.nlm.nih.gov/20635774/; (A review of "Twenty-nine Random Control Trials were included in three separate meta-analyses. Results showed multi-modal CBT was more effective than no primary care treatment (d =0.59), and primary care treatment-as-usual (TAU) (d = 0.48) for anxiety and depression symptoms."). See, e.g., Twomey, C., O'Reilly, G. and Byrne, M. Effectiveness of cognitive behavioural therapy for anxiety and depression in primary care: a meta-analysis, Family Practice, Volume 32, Issue 1, February 2015, pp. 3–15, https://doi.org/10.1093/fampra/cmu060. The political taint is so strong

that some providers reportedly fail to offer and engage in CBT therapy with depressed/anxious gender dysphoric patients for fear of being attacked as engaging in "conversion" therapy. Again, the institutionalization of medical negligence (e.g., confirmation bias) harms vulnerable patients.

44. PROPER INVESTIGATIONS OF DECEPTIVE MISCONDUCT. Ideological over-reach can lead to unethical misconduct and licensing violations. Misrepresenting medical-scientific research, deceptively hiding methodological errors, or failing to honestly report ongoing international controversies to courts, patients, or guardians should be properly investigated as misconduct. Licensing boards and professional associations produce and should properly enforce ethics rules and requirements governing the conduct of health care professionals to protect the rights of patients and parents.

45. THE ACTUAL PREVALENCE OF GENDER DYSPHORIA and PATIENTS THAT IDENTIFY AS GENDER DISCORDANT ("transgender") IS UNKNOWN BUT IT APPEARS TO BE INCREASING AT A RAPIDLY ACCELERATING RATE THUS SUPPORTING AN ALTERNATIVE HYPOTHESIS OF SOCIAL CONTAGION: Estimates reported in in the DSM-V were between 0.005% to 0.014% for adult males and 0.002% to 0.003% for adult females. Thus, gender dysphoria was, until just a few years ago, a very rare condition. It is currently unknown whether these DSM estimates were falsely low due to under-reporting or:

- whether changing societal acceptance of transgendered identity and the growing number of medical centers providing interventions for gender dysphoria has led to increased reporting of persons who identify as transgender ;
- whether the reported educational programs aggressively promoting "non-binary" identification to elementary to high school students to college students have greatly increased the numbers of youth adopting a transgender identity;

- whether the reported wave of "trans You Tube influencers" watched by millions each day as they aggressively "sell" the transgender lifestyle has added to a social contagion effect with vulnerable lonely, depression, anxious, or autistic youth; or
- whether other causal processes are at play.

A key unanswered research question is whether a social contagion process is leading to vast and rapid increases in the numbers of patients identifying as gender discordant ("transgender"). How many of the new waves of thousands of cases are 'false reports' that will dissipate with time and normal development over time? For example, the Gender Identity Development Service in the United Kingdom, which treats only children under the age of 18, reported that it received 94 referrals of children in 2009/2010 and 1,986 referrals of children in 2016/2017, a relative increase of 2,000%. See "GIDS referrals figures for 2016/17," Gender Identity Development Service, GIDS. NHS.uk (undated), http://gids.nhs.uk/sites/default/files/content_uploads/referralfigures-2016-17.pdf.

Reportedly, similar social contagion processes led to tens of thousands of patients and families being harmed by controversial diagnoses such as multiple personality disorder (MPD) and controversial interventions including recovered memory therapy (RMT). RMT and MPD patients, once considered extremely rare (some 300 MPD patients reported worldwide prior to the 1980s-1990s social contagion epidemic) erupted into a flood of tens of thousands of patients and affected families in the 1990s. These very controversial disorders and treatments were greatly reduced by dozens of civil lawsuits against RMT-MPD therapists, international news exposure of scientific evidence debunking these notions, and international news reporting of the civil litigation, licensing prosecutions, and licensing revocations of well-known RMT-

MPD practitioners. (See, e.g., Belluck, P. Memory Therapy Leads to a Lawsuit and Big Settlement [$10.6 Million], The New York Times, Page 1, Column 1, Nov. 6, 1997; Pendergrast, M. (2017). The repressed memory epidemic: How it happened and what we need to learn from it. New York, NY: Springer).

Recent data indicates that the number of people seeking care for gender dysphoria is rapidly increasing with some estimates as high as 20-fold and more. See Chen, M., Fuqua, J. & Eugster, E. A. Characteristics of Referrals for Gender Dysphoria Over a 13-Year Period. Journal of Adolescent Health 58, 369-371, doi:https://doi.org/10.1016/j.jadohealth.2015.11.010 (2016); 4. "GIDS referrals figures for 2016/17," Gender Identity Development Service, GIDS.NHS.uk (undated), http://gids.nhs.uk/sites/default/files/content_uploads/referral-figures-2016-17.pdf). See Zucker K. J. (2017). Epidemiology of gender dysphoria and transgender identity. *Sexual health*, *14*(5), 404–411. https://doi.org/10.1071/SH17067. Data from England show *increases of 4,000%* for female to male patients and in America data show *increases of 20,000%* for young women (e.g. from .01 to 2%). Estimates vary considerably in relation to how sex-gender identity discordance is defined. See Zhang, Q., Goodman, M., Adams, N., Corneil, T., Hashemi, L., Kreukels, B., Motmans, J., Snyder, R., & Coleman, E. (2020). Epidemiological considerations in transgender health: A systematic review with focus on higher quality data. *International journal of transgender health*, *21*(2), 125–137. https://doi.org/10.1080; Poteat, T., Rachlin, K., Lare, S., Janssen, A. & Devor, A. in *Transgender Medicine: A Multidisciplinary Approach* (eds Leonid Poretsky & Wylie C. Hembree) 1-24 (Springer International Publishing, 2019); Flores AR, Herman JL, Gates, GJ, Brown TNT. How Many Adults Identify as Transgender in the United States? Los Angeles, CA: The Williams Institute; 2016. https://williamsinstitute.law.ucla.edu/wp-content/uploads/Trans-Adults-US-Aug-2016.pdf. Accessed April 28, 2021.

46. EVIDENCE SUPPORTS THE HYPOTHESIS THAT GENDER IDENTITY IS *NOT* GENETICALLY OR BIOLOGICALLY DETERMINED: There is strong disconfirming evidence (e.g., Popperian falsifiability) against the theory that gender identity is determined at or before birth and is unchangeable. This comes from A) identical twin studies where siblings share genetic complements and prenatal environmental exposure but have differing gender identities. See Heylens, G. et al. Gender identity disorder in twins: a review of the case report literature. J Sex Med 9, 751-757, doi:10.1111/j.1743-6109.2011.02567.x (2012) and B) the very recent and massive increase in the numbers of GD patients over a very short time span. This argues against a biological-genetic hypothesis. See Leinung MC, Joseph J. Changing Demographics in Transgender Individuals Seeking Hormonal Therapy: Are Trans Women More Common Than Trans Men? Transgend Health. 2020 Dec 11;5(4):241-245. doi: 10.1089/trgh.2019.0070. PMID: 33644314; PMCID: PMC7906237.

47. REPLICATED RESEARCH EVIDENCE SUPPORTS THE HYPOTHESIS THAT GENDER IDENTITY IS *NOT* IMMUTABLE: Further evidence that gender identity is not fixed and immutable comes from established peer reviewed literature demonstrating that the vast majority (80-95%) of children who express gender dysphoria revert to a gender identity concordant with their biological sex by late adolescence. This natural developmental "cure" of gender dysphoria requires no direct "treatment" and prevents the hormonal and surgical destruction of normal, healthy organs and bodily processes (e.g. prevents sterilization of the child). See Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. Front Psychiatry. 2021 Mar 29;12:632784. doi: 10.3389/fpsyt.2021.632784. PMID: 33854450; PMCID: PMC8039393. It is not currently known whether individuals with gender dysphoria persistence have differing etiologies or severity of precipitating factors compared to desisting individuals.

See Drummond, K. D., Bradley, S. J., Peterson-Badali, M. & Zucker, K. J. A follow-up study of girls with gender identity disorder. Dev Psychol **44**, 34-45, doi:10.1037/0012-1649.44.1.34 (2008); Steensma, T. D., McGuire, J. K., Kreukels, B. P., Beekman, A. J. & Cohen-Kettenis, P. T. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry **52**, 582-590, doi:10.1016/j.jaac.2013.03.016 (2013).

48. VIRTUALLY ALL TRANSGENDER PATIENTS ARE BORN WITH HEALTHY NORMAL SEX ORGANS AND NO KNOWN BRAIN OR GENETIC ABNORMALITIES: Most people with gender dysphoria, do not have a disorder of sexual development. As documented in their medical record, such patients typically have normally formed sexual organs. The presence of normal, functional sex organs prior to the initiation of hormone administration or surgical "transition" operations is typical in transgender patients. I note that both hormonal treatments and surgery to remove healthy, normal organs (the genitals of GD patients) destroy the function of healthy organs (e.g., producing the life-long sterilization of GD patients). Such injurious "treatments" are very controversial and occur nowhere else in medicine that I am aware of with the exception of requests for the amputation of healthy limbs in patients suffering from the very controversial "body integrity identity disorder". See Elliott, T., Body Dysmorphic Disorder, Radical Surgery and the Limits of Consent**,** *Medical Law Review*, Volume 17, Issue 2, Summer 2009, Pages 149–182, https://doi.org/10.1093/medlaw/fwp001. In 2000 there was a media furor when it was disclosed that a Scottish surgeon had operated upon two adult male patients reportedly suffering from a rare form of a psychological condition known as body integrity identity disorder, in each case amputating a healthy leg. Since then, the question of whether such surgery is ethically or legally permissible has been a matter of debate. The subject raises issues

as to the extent to which it is proper to treat adults with psychiatric or psychological disorders with radical surgery, particularly where the appropriate diagnosis and treatment of the underlying disorder is uncertain or disputed. Similarly, gender transition interventions also involve treating patients "with psychiatric or psychological disorders with radical surgery, where the appropriate diagnosis and treatment of the underlying disorder is uncertain or disputed."

The primary use of psychotherapy as a means to treat body dysmorphic disorder contrasts with the approaches used by the gender transition industry. See Hadley, S. J., Greenberg, J., & Hollander, E. (2002). Diagnosis and treatment of body dysmorphic disorder in adolescents. *Current psychiatry reports*, *4*(2), 108–113. https://doi.org/10.1007/s11920-002-0043-4; Allen, A., & Hollander, E. (2000). Body dysmorphic disorder. *The Psychiatric clinics of North America*, *23*(3), 617–628. https://doi.org/10.1016/s0193-953x(05)70184-2.

49. THE ETIOLOGY (CAUSE) OF GENDER DYSPHORIA IS CURRENTLY UNKNOWN and the "TREATMENTS" are of UNCERTAIN EFFICACY. The current theories and treatments remain experimental and controversial. The etiology of gender dysphoria in individuals with sex-gender identity discordance remains unknown. Alternative hypotheses include some as yet unidentified biological cause, prenatal hormone exposure, genetic variation, postnatal environmental influences, family dynamics, other forms of mental illness, an abnormal detour from developmental identity processes, social contagion effects on suggestible-vulnerable subjects, or a combination of multiple factors. Based upon the available evidence, it is most likely that sex-gender identity discordance is multifactorial with both genetic and environmental influences, differing in both kind and degree in any affected individual. Importantly, these potential contributing factors are hypothesized to be contributory, but not determinative of the condition.

See Saleem, Fatima, and Syed W. Rizvi. "Transgender Associations and Possible Etiology: A Literature Review." Cureus 9, no. 12 (2017): e1984.

50. THE CONCEPT OF "NEUROLOGICAL SEX" IS EXPERIMENTAL, UNVERIFIED, HAS NO KNOWN ERROR RATE and is NOT ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY. The recently coined concept of "neurological sex" as a distinct entity or a basis for classifying individuals as male or female has no scientific justification. Limited emerging data has suggested structural and functional differences between brains from normal and transgender individuals. These data do not establish whether these differences are innate and fixed or acquired and malleable. The remarkable neuronal plasticity of the brain is well known, well documented, and has been studied extensively in gender-independent contexts related to health and disease, learning, and behavior. See Fatima Yousif Ismail, Ali Fatemi, and Michael V. Johnston, "Cerebral Plasticity: Windows of Opportunity in the Developing Brain," European Journal of Paediatric Neurology 21, no. 1 (2017).

51. GENDER IDENTITY IDEOLOGY IS A POLITICAL, NOT SCIENTIFIC THEORY. A key alternative investigative hypothesis in efforts to understand the rise of reports of gender discordance and social-political-medical attempts to create a transgender movement is that such ideas are not based upon sound scientific biological, genetic, or related principles and data but rather are based upon ideology and driven by political advocacy. Although worldviews among scientists and physicians differ widely (similar to society at large), science must remain firmly grounded in testable, valid, and reliable assessments of physical reality—not ideologically tainted perceptions and belief systems. The inherent link between human sexual biology and teleology (e.g. human reproduction) is self-evident and fixed. Breithaupt H. The science of sex.

EMBO Rep. 2012;13(5):394. Published 2012 May 1. doi:10.1038/embor.2012.45. Activists often support clearly contradictory theories and arguments at the same time (e.g. the claim that Gender Dysphoria (GD) and "trans identity" are" immutable", "genetic", or based on "brain structures" while simultaneously claiming GD is also "fluid" and thus capable of changing on a daily basis). That is perhaps because the gender transition industry gains support from controversial ideological foundations. (See, e.g., Pluckrose, and Lindsay, J., Cynical Theories: How Activist Scholarship Made Everything about Race, Gender, and Identity—and Why This Harms Everybody, Pitchstone Publishing, August 25, 2020).

52. GENDER IDENTITY IDEOLOGY HAS NO SCIENTIFIC BASIS, HAS NEVER BEEN ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY, and HAS NO KNOWN NOR PUBLISHED ERROR RATE. The political-ideological claims of proponents of transgenderism, which include opinions such as "gender identity is the primary factor determining a person's sex," "gender is the only true determinant of sex," and individuals have "sex assigned at birth" must be viewed in their proper ideological context. There is no scientific basis for redefining sex on the basis of a person's subjective, psychological sense of "gender".

53. IN CONTRAST TO "TRANSGENDER" IDEOLOGY, THE BIOLOGICAL BASIS OF SEX IS FIRMLY GROUNDED IN SCIENCE, ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY, AND HAS A VERY LOW ERROR RATE: The prevailing, constant, tested, proven, and accurate designation of sex as a biological trait grounded in the inherent purpose of male and female anatomy and as manifested in the appearance of external genitalia at birth remains the proper scientific and medical standard. Redefinition of the classification and meaning of sex based upon pathologic variation is not established medical fact. See, e.g.,

Mittwoch, U. (2013), Sex determination. EMBO reports, 14: 588-592. https://doi.org/10.1038/embor.2013.84

54. THE ETHICAL FOUNDATIONS of MEDICINE—FIRST DO NO HARM: The fundamental purpose of the practice of medicine is to treat disease and alleviate suffering. An essential tenet of medical practice is to avoid doing harm in the process. Efforts to rely upon clear, valid, reliable, and definitive evidence on how to best accomplish treatment goals is the essential ethical, professional, scientific, and clinical goals of physicians. The gender transition industry violates this essential principle by using experimental treatments on vulnerable populations without properly informing them of the actual risks and limitations of the treatments. See Jonson AR, Siegler M, Winslade, WJ: Clinical Ethics, New York: McGraw Hill, 1998.

55. THE ETHICAL FOUNDATIONS of MEDICINE REQUIRE US TO STRIVE TO HELP THOSE IN DISTRESS WITH COMPASSION, KINDNESS, and EMPATHY WITHOUT VIOLATING PATIENTS' and PARENTS' RIGHTS BY ENGAGING IN EXPERIMENTAL, UNPROVEN INTERVENTIONS LEADING TO PERMANENT DAMAGE TO MANY PATIENTS—INCLUDING STERILIZATION: Persons with gender dysphoria as defined in the DSM-V report experiencing significant psychological distress related to their condition with elevated risk of depression, suicide, and other morbidities. Thus, attempts to provide effective medical care to affected persons are clearly warranted. Efforts to effectively treat persons with gender dysphoria require respect for the inherent dignity of those affected, sensitivity to their suffering, and maintenance of objectivity in assessing etiologies and long-term outcomes. In my opinion, the use of unproven, experimental treatments on vulnerable patients and the publication of grossly methodologically defective research are violations of the ethical foundations of medicine.

56. THREE CURRENT APPROACHES FOR MANAGING GENDER DYSPHORIA: To date, three approaches have been proposed for treating children with gender dysphoria. See Zucker, K. J. On the "natural history" of gender identity disorder in children. J Am Acad Child Adolesc Psychiatry 47, 1361-1363, doi:10.1097/CHI.0b013e31818960cf (2008).) The first approach, often referred to as "conversion" or "reparative therapy," is directed toward actively supporting and encouraging children to identify with their biological sex. The second "neutral" or "watchful waiting" approach, motivated by understanding of the natural history of transgender identification in children, is to neither encourage nor discourage transgender identification, recognizing that the vast majority of affected children if left alone are likely to eventually realign their reports of gender identification with their sex. This approach may also include the use of scientifically validated treatments (e.g. CBT) for the patient's anxiety, depression, social skills deficits or other issues. See van Bentum, J. S., van Bronswijk, S. C., Sijbrandij, M., Lemmens, L., Peeters, F., Drukker, M., & Huibers, M. (2021). Cognitive therapy and interpersonal psychotherapy reduce suicidal ideation independent from their effect on depression. *Depression and anxiety*, 10.1002/da.23151. Advance online publication. https://doi.org/10.1002/da.23151; Gallagher, M. W., Phillips, C. A., D'Souza, J., Richardson, A., Long, L. J., Boswell, J. F., Farchione, T. J., & Barlow, D. H. (2020). Trajectories of change in well-being during cognitive behavioral therapies for anxiety disorders: Quantifying the impact and covariation with improvements in anxiety. *Psychotherapy (Chicago, Ill.)*, *57*(3), 379–390. https://doi.org/10.1037/pst0000283. The third, "affirming," approach is to actively encourage children to embrace transgender identity with social transitioning followed by hormonal therapy leading to potential surgical interventions and life-long sterilization. See Walch A, Davidge-Pitts C, Safer JD, Lopez X, TangprichaV, Iwamoto SJ. Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed

Discrimination: A Policy Perspective J Clin Endocrinol Metab. 2021;106(2):305-308. doi:10.1210/clinem/dgaa816**.**

57. THE "WATCHFUL WAITING" TREATMENT MODALITY INVOLVES NO MEDICAL INTERVENTION AND IS CURRENTLY THE BEST SCIENTIFICALLY SUPPORTED INTERVENTION FOR YOUNG CHILDREN REPORTING GENDER DYSPHORIA: Desistance (i.e. realignment of expressed gender identity to be concordant with sex) provides the greatest lifelong benefit, is the outcome in the vast majority of patients, and should be maintained as a desired goal. Any scientifically untested intervention that unnecessarily interferes with the likelihood of a normal, non-traumatic, developmental resolution of gender dysphoria is unwarranted and potentially harmful. The gender affirming approach, which includes use of a child's preferred pronouns, use of sex-segregated bathrooms, other intimate facilities and sleeping accommodations corresponding to a child's gender identity, has limited, "very weak," "sparse" scientific support for short-term alleviation of dysphoria and *no long-term outcomes data demonstrating superiority over the other approaches*. (See national reviews of England, Sweden, Finland, the Cochrane review, the Griffin review, the Carmichael review and others). Claims that the other approaches have been scientifically disproven are simply false. Decades of peer-reviewed, published scientific research, including the pioneering work of Dr. Kenneth Zucker, have supported the efficacy of the "watchful waiting" approach for the majority of patients experiencing gender dysphoria. See Zucker, K. J. On the "natural history" of gender identity disorder in children. J Am Acad Child Adolesc Psychiatry 47, 1361-1363, doi:10.1097/CHI.0b013e31818960cf (2008); Bradley, S. J. & Zucker, K. J. Gender Identity Disorder: A Review of the Past 10 YearsG. Journal of the American Academy of Child & Adolescent Psychiatry 36, 872-880, doi:10.1097/00004583-199707000-00008.). In sum, the treatment

protocols and recommendations of politically influenced, non-science associations (WPATH, Pediatrics Assn, APA) who engaged in "voting", consensus-seeking methodologies (not science) are not accepted by the relevant *scientific* community, are not based upon competent-credible, methodologically sound science, and have no known, nor published, error rate.

58. THE HARMFUL EFFECTS OF "AFFIRMATIVE" TREATMENTS—INCLUDING PUBERTAL SUPPRESSION—ARE ESTABLISHED and ACCEPTED BY THE RELEVANT SCIENTIFIC COMMUNITY: "To sum up how puberty suppression works, a thought experiment might be helpful. Imagine two pairs of biologically and psychologically normal identical twins—a pair of boys and a pair of girls—where one child from each pair undergoes puberty suppression and the other twin does not. Doctors begin administering GnRH analogue treatments for the girl at, say, age 8, and for the boy at age 9. Stopping the gonadal hormone pathway of puberty does not stop time, so the puberty- suppressed twins will continue to age and grow—and because adrenal hormones associated with puberty will not be affected, the twins receiving GnRH analogue will even undergo some of the changes associated with puberty, such as the growth of pubic hair. However, there will be major, obvious differences within each set of twins. *The hormone suppressed twins' reproductive organs will not mature*: the testicles and penis of the boy undergoing puberty suppression will not mature, and the girl undergoing puberty suppression will not menstruate. The boy undergoing puberty suppression will have less muscle mass and narrower shoulders than his twin, while the breasts of the girl undergoing puberty suppression will not develop. The boy and girl undergoing puberty suppression will not have the same adolescent growth spurts as their twins. *So all told, by the time the untreated twins reach maturity, look like adults, and are biologically capable of having children, the twins undergoing puberty suppression will be several inches shorter, will physically look more androgynous and*

childlike, and will not be biologically capable of having children. This is a thought experiment, but it illustrates some of the effects that puberty suppression would be expected to have on the development of a growing adolescent's body." See Hruz, PW, Mayer, LS, and McHugh, PR, "Growing Pains: Problems with Puberty Suppression in Treating Gender Dysphoria," The New Atlantis, Number 52, Spring 2017 pp. 3-36.

59. THE ENDOCRINE SOCIETY RECOGNIZES THAT THE QUALITY OF EVIDENCE FOR "AFFIRMATIVE" TREATMENTS IS CURRENTLY *"LOW OR VERY LOW" ("estimate of effect is very uncertain"*). There is no general acceptance of these treatments in the relevant scientific community. The error rate is unknown and could be very high. The Endocrine Society published 2009 clinical guidelines for the treatment of patients with persistent gender dysphoria. See Hembree, W. C. et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 94, 3132-3154, doi:10.1210/jc.2009-0345 (2009). The recommendations include temporary suppression of pubertal development of children with GnRH agonists (hormone blockers normally used for children experiencing precocious puberty) followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. In developing these guidelines, the authors assessed the quality of evidence supporting the recommendations made with use of the GRADE (Recommendations, Assessment, Development, and Evaluation) system for rating clinical guidelines. As directly stated in the Endocrine Society publication, *"the strength of recommendations and the quality of evidence was low or very low*." According to the GRADE system, low recommendations indicate that "[f]urther research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate." Very low recommendations mean that **"**any estimate of effect is very uncertain." (See

Guyatt G H, Oxman A D, Vist G E, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations BMJ 2008; 336 :924 doi:10.1136/bmj.39489.470347.AD). An updated set of guidelines was published in September of 2017. See Hembree, W. C. et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, doi:10.1210/jc.2017-01658 (2017). The low quality of evidence presented in this document persists to the current day, as the controversy over these "treatments" is accelerating in recent years.

60. THE WPATH GUIDELINES (7th version) NOTE SERIOUS LIMITATIONS OF THE EXISTING SCIENTIFIC DATA: Clinical Practice Guidelines published by the World Professional Association for Transgender Health (WPATH) - (an advocacy organization whose positions are based on voting and not a scientific, evidence-based process) which is currently in its 7th iteration, similarly, though less explicitly, acknowledge the limitation of existing scientific data supporting their recommendations given and "the value of harm-reduction approaches". Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., Fraser, L., Green, J., Knudson, G., Meyer, W. J., Monstrey, S., Adler, R. K., Brown, G. R., Devor, A. H., Ehrbar, R., Ettner, R., Eyler, E., Garofalo, R., Karasic, D. H., . . . Zucker, K. (2012). Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. International Journal of Transgenderism, 13(4), 165–232. https://doi.org/10.1080/15532739.2011.700873.

61. ADMINISTERING HORMONES TO A CHILD WHOSE GENDER DYSPHORIA IS HIGHLY LIKELY (80%+) TO RESOLVE IS RISKY, UNSCIENTIFIC and UNETHICAL. Iatrogenic damages, including life-long sterility, stunted growth, increased heart attack risk, etc.,

are often irreversible. Treatment of gender dysphoric children who experience persistence of symptoms with hormones (pubertal suppression and cross-hormone therapy) carries significant risk. It is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment impairs fertility and often result in sterility, which in many cases is irreversible. See Nahata, L., Tishelman, A. C., Caltabellotta, N. M. & Quinn, G. P. Low Fertility Preservation Utilization Among Transgender Youth. Journal of Adolescent Health 61, 40-44, doi:https://doi.org/10.1016/j.jadohealth.2016.12.012 (2017)). Emerging data also show that treated patients have lower bone density which may lead to increased fracture risk later in life. See Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M. & Rotteveel, J. Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. The Journal of Clinical Endocrinology & Metabolism 100, E270-E275, doi:10.1210/jc.2014-2439 (2015)). Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease. See Seal, L. J. A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria. Annals of Clinical Biochemistry 53, 10-20, doi:10.1177/0004563215587763 (2016); Banks, K., Kyinn, M., Leemaqz, S. Y., Sarkodie, E., Goldstein, D., & Irwig, M. S. (2021). See also, Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults. *Hypertension (Dallas, Tex.: 1979)*, HYPERTENSIONAHA12016839. Advance online publication. https://doi.org/10.1161/HYPERTENSIONAHA.120.16839; Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., Hunkeler, E., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D., Silverberg, M. J., Safer, J., Slovis, J., Tangpricha, V., & Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular

Events in Transgender Persons: A Cohort Study. *Annals of internal medicine*, *169*(4), 205–213. https://doi.org/10.7326/M17-2785; Spyridoula Maraka, Naykky Singh Ospina, Rene Rodriguez-Gutierrez, Caroline J Davidge-Pitts, Todd B Nippoldt, Larry J Prokop, M Hassan Murad, Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis, *The Journal of Clinical Endocrinology & Metabolism*, Volume 102, Issue 11, 1 November 2017, Pages 3914–3923, https://doi.org/10.1210/jc.2017-01643.

62. LONG TERM EFFECTS ARE UNKNOWN. Such treatments are not generally accepted by the relevant scientific community and have no known nor published error rate. Since strategies for the treatment of transgender children as summarized by the Endocrine Society guidelines are relatively new, long-term outcomes are unknown. Evidence presented as support for short-term reductions in psychological distress following social transition in a "gender affirming" environment remains inconclusive. When considered apart from advocacy-based agendas, multiple potential confounders are evident. The most notable deficiencies of existing research are the absence of proper control subjects and lack of randomization in study design. See Hruz, P. W. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q* 87, 34-42, doi:10.1177/0024363919873762 (2020). Although appropriate caution is warranted in extrapolating the outcomes observed from prior studies with current treatments, adults who have undergone social transition with or without surgical modification of external genitalia continue to have *rates of depression, anxiety, substance abuse and suicide far above the background population*. See Adams, N., Hitomi, M. & Moody, C. Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature. Transgend Health 2, 60-75, doi:10.1089/trgh.2016.0036 (2017); see also Dhejne, C. et al. Long-

term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 6, e16885, doi:10.1371/journal.pone.0016885 (2011)).

63. MEDICAL TREATMENTS CONTRARY TO THE SCIENCE COULD RESULT IN IRREVERSIBLE HARMS TO MANY PATIENTS WHO WOULD OTHERWISE HAVE RECOVERED NATURALLY FROM GENDER DYSPHORIA: Of particular concern is the likelihood that naively requested gender transition "treatments" and social changes could interfere with known very high rates of natural-untreated resolution of sex-gender discordance. Any activity that encourages or perpetuates transgender persistence for those who would otherwise desist could cause significant harm, particularly in light of the current treatment paradigm for persisting individuals. As noted, sterility can often be expected with hormonal or surgical disruption of normal gonadal function. See Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotaling JM. Fertility concerns of the transgender patient. Transl Androl Urol. 2019 Jun;8(3):209-218. doi: 10.21037/tau.2019.05.09. PMID: 31380227; PMCID: PMC6626312.

64. YOUNG CHILDREN and PARENTS ARE OFTEN NOT PROPERLY INFORMED or ARE NOT COMPETENT TO GIVE INFORMED CONSENT TO PROCEED WITH EXPERIMENTAL, HAZARDOUS TREATMENTS THAT COULD POTENTIALLY RESULT IN PERMANENT STERILITY: This is a particularly concerning issue given that children are likely to be incapable of giving truly informed consent. See Geier, C. F. Adolescent cognitive control and reward processing: Implications for risk taking and substance use. Hormones and Behavior 64, 333-342, doi:https://doi.org/10.1016/j.yhbeh.2013.02.008 (2013). This concern remains valid when applied to hormonal or surgical treatments that will result in lifelong sterility. In addition, parents are often manipulated and coerced by misinformed political activists or providers who threaten them with dire warnings that the only two options are "treatment or suicide".

These "threats" ignore data that challenge this biased assumption. See D'Angelo, R., Syrulnik, E., Ayad, S. *et al.* One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Arch Sex Behav* 50**,** 7–16 (2021). https://doi.org/10.1007/s10508-020-01844-2

65. SOCIAL CONTAGION HAS BEEN IMPROPERLY IGNORED BY PROVIDERS: Social and psychological support with dignity for adolescents with gender dysphoria does not necessitate acceptance of a unproven, experimental understanding of human sexuality. Rather, policy requirements including social contagion promoting educational processes that can increase the prevalence and persistence of transgender identification have significant potential for inducing long-term harm to affected children.

66. COMPETENT, METHODOLOGICALLY SOUND, LONG-TERM TREATMENT OUTCOME RESEARCH ON GENDER DYSPHORIA INTERVENTIONS HAS NEVER BEEN DONE: There remains a significant and unmet need to improve our understand of the biological, psychological, and environmental basis for the manifestation of patient reports of discordance of gender identity and biological sex in affected individuals. (Olson-Kennedy, J. et al. Research priorities for gender nonconforming/transgender youth: gender identity development and biopsychosocial outcomes. Current Opinion in Endocrinology, Diabetes and Obesity 23, 172-179, (2016)). In particular, there is a concerning lack of randomized controlled trials comparing outcomes of youth with gender dysphoria who are provided public encouragement for "affirming" social gender transition and how such transitioning affects the usual and natural progression to resolution of gender dysphoria in most affected children. Such studies can be ethically designed and executed with provisions for other dignity affirming measures to both treatment groups. See Sugarman J. Ethics in the design and conduct of clinical trials. Epidemiol Rev.

2002;24(1):54-8. doi: 10.1093/epirev/24.1.54. PMID: 12119856; And https://clinicalcenter.nih.gov/recruit/ethics.html

67. DUE TO THE LACK OF QUALITY, CREDIBLE SUPPORTIVE RESEARCH GENDER AFFIRMING INTERVENTIONS REMAIN EXPERIMENTAL and HIGHLY CONTROVERSIAL. Gender identity is consolidated during puberty and adolescence as young people's bodies become more sexually differentiated and mature. How this normally happens is not well understood, so it is imperative to be cautious about interfering with this complex natural process. Far from being cautious and prudent in using puberty blockers to treat gender dysphoria, too many providers engaged in gender affirming medical interventions are conducting an unethical and risky experiment that does not come close to the ethical standards demanded in other areas of medicine. No one really knows all the potential consequences of puberty blocking as a treatment for gender dysphoria, but there are some known effects of pubertal suppression on children who are physiologically normal, and these carry long-term health risks. Children placed on puberty blockers have slower rates of growth in height, and an elevated risk of low bone-mineral density. Another possible effect of blocking normally timed puberty is alteration of normal adolescent brain maturation. (See Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric disease and treatment*, *9*, 449–461. https://doi.org/10.2147/NDT.S39776).

When followed by cross-sex hormones, known and potential effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease. Tragically, those children who persist in their transgender identity and take puberty blockers and cross-sex hormones are *expected to become sterile*. Given what we already know about puberty blocking and how much remains unknown, it

is not surprising that the use of GnRH analogues for puberty suppression in children with gender dysphoria is not FDA-approved. The off-label prescription of these drugs is legal *but unethical* outside the setting of a carefully controlled and supervised clinical trial. See Hruz, Mayer, and McHugh, "Growing Pains." Trans activist professionals act as if there is a firm scientific consensus that it is safe and effective to treat gender dysphoria by using GnRH analogues to suppress normal puberty indefinitely. But this is far from the reality, as I, together with Mayer and McHugh, have pointed out: "Whether puberty suppression is safe and effective when used for gender dysphoria remains unclear and unsupported by rigorous scientific evidence." Thus, it is not generally accepted by the relevant scientific community. Instead of regarding puberty blocking as a "prudent and scientifically proven treatment option," courts of law, parents, and the medical community *should view it as a "drastic and experimental measure*." (See Hruz, Mayer, and McHugh, 2017.) The use of any experimental medical treatment on children calls for "especially intense scrutiny, since children cannot provide proper legal consent to experimental medical treatments—especially treatments that may harm natural gender processes and produce sterility.

The rapid acceptance of puberty suppression as a treatment for gender dysphoria with little scientific support or scrutiny should raise concerns about the welfare of the children who receive such treatments. In particular, we should question the claim that it is both physiologically and psychologically "reversible." This includes the alteration of a temporally dependent developmental process. After an extended period of pubertal suppression one cannot "turn back the clock" and reverse changes in the normal coordinated pattern of adolescent psychological development and puberty. (See Hruz, Mayer, and McHugh, "Growing Pains, The New Atlantis: A Journal of Technology and Society, Spring 2017, pg 3-36; see also Vijayakumar N, Op de Macks

Z, Shirtcliff EA, Pfeifer JH. Puberty and the human brain: Insights into adolescent development. Neurosci Biobehav Rev. 2018 Sep;92:417-436. doi: 10.1016/j.neubiorev.2018.06.004. Epub 2018 Jul 1. PMID: 29972766; PMCID: PMC6234123; see also Choudhury S, Culturing the adolescent brain: what can neuroscience learn from anthropology?, *Social Cognitive and Affective Neuroscience*, Volume 5, Issue 2-3, June/September 2010, Pages 159–167, https://doi.org/10.1093/scan/nsp030

68. ACTIVIST ATTEMPTS TO CONTROL PUBLIC DISCUSSION ARE HARMFUL TO SCIENCE: The controversies regarding the risks and potential dangers of the transgender industry cannot be resolved by "cancel culture." As Steven Levine, MD of Case Western has noted, "Among psychiatrists and psychotherapists who practice in the area, *there are currently widely varying views* concerning both the causes of, and appropriate therapeutic responses to, gender dysphoria in children. Dr. Levine went on to state, "Existing studies do not provide a basis for a scientific conclusion as to which therapeutic response results in the best long-term outcomes for affected individuals." Although political advocates have asserted that the "affirmation therapy" model is accepted and agreed with by the overwhelming majority of mental health professionals, many respected academics and providers in the field strongly disagree. For example, J. Cantor, Ph.D. (McGill) published the following opinion in 2019, "almost all clinics and professional associations in the world" do not use "gender affirmation" for prepubescent children and instead "delay any transitions until after the onset of puberty." See J. Cantor (2019), Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy, J. of Sex& Marital Therapy, 1, DOI: 10.1080.0092623X.2019.1698481.

69. In the midst of this ongoing international, raging controversy, transgender and allied political activists have attempted to silence open public debate on the risks and benefits of

transgender medical procedures and political ideologies. For example, Ryan Anderson, Ph.D., a policy analyst, wrote a book analyzing the scientific and policy issues involved in assessing the risks and benefits of the current practices of the transgender treatment industry. See Anderson, R., *When Harry Became Sally: Responding to the Transgender Moment*, Encounter Books. Despite widespread scientific interest and positive reviews, the book was banned from sale by the Amazon Corporation. Too many lives are at stake for such blatant suppression of open scientific discussion. Several positive reviews of Dr Ryan's book were posted by notable members of the relevant scientific-ethical community including: Paul McHugh, MD, University Distinguished Professor of Psychiatry, Johns Hopkins University School of Medicine (Dr McHugh was trained at Harvard College and Harvard Medical School. He served as the Chairman of Psychiatry at Johns Hopkins Medical School for decades) and Melissa Moschella, PhD, who served at Columbia University as Director of the Center for Biomedical Ethics in the Department of Medicine and currently at The Catholic University of America. (Dr. Moschella was trained at Harvard College and her PhD is from Princeton University) and Maureen Condic, Associate Professor of Neurobiology and Adjunct Professor of Pediatrics, University of Utah Medical School. (Dr. Condic's training includes a B.A. from the University of Chicago, and a Ph.D. from the University of California, Berkeley) and John Finnis, Ph.D., Professor of Law at Oxford University for 40 years, now Emeritus. (LL.B. from Adelaide University (Australia) and Ph.D. in 1965 from Oxford University as a Rhodes Scholar at University College Oxford.)

International experts from a variety of relevant fields consider the issue of proper and harmful transgender treatments to be a serious controversy that must not be silenced. Other scholars in this contentious field have been threatened and/or silenced by the political and ideo-

logical allies of the gender transition industry. Consider, for example, the case of Alan Josephson, MD, a distinguished psychiatrist. See Kearns, M., Gender Dissenter Gets Fired, National Review, Jan 12, 2019. "Allan M. Josephson is a distinguished psychiatrist who, since 2003, has transformed the division of child and adolescent psychiatry and psychology at the University of Louisville from a struggling department to a nationally acclaimed program. In the fall of 2017 he appeared on a panel at the Heritage Foundation and shared his professional opinion on the medicalization of gender-confused youth. The university responded by demoting him and then effectively firing him." See https://www.nationalreview.com/2019/07/allen-josephson-gender-dissenter-gets-fired/. Theories in the midst of an international firestorm of controversy are clearly not "generally accepted" by the relevant scientific community. The ongoing attempts to ban books and aggressively silence academic debate or "cancel" professionals with alternative views are clear demonstrations of the ongoing and intense controversies surrounding the gender transition industry.

70. Consider also the example of Dr. Lisa Littman at Brown University Medical School. Dr. Littman conducted extensive surveys to assess the experiences of parents involved in an online community for parents of transgender children or "gender skeptical" parents and children. There were 256 completed surveys. Their children were mostly adolescents or young adults. The parents reported that about 80 percent of their (mostly adolescent) children announced their transgender identity "out of the blue" without the long-term history generally associated with gender dysphoria. The parents also reported that transgender identity was linked with mental health issues (an often repeated, reliable finding in multiple studies from multiple nations). The parents also reported that after their children came out as transgender, their children's mental health worsened, as did relationships with family members. The parents also reported a *decline*

in the children's social adjustment after the announcement (e.g., more isolation, more distrust of non-transgender information sources, etc.).

The publication of the Littman paper was greeted by the outrage of trans activists who denounced the paper and Dr. Littman, calling it "hate speech and transphobic." Brown University had initially produced a press release for the paper stating the Littman research provided bold new insights into transgender issues. Once the political attacks began, the University removed it from their announcements. Fortunately, in this case, there was also a counter-outcry from scientists decrying Brown University and the political activists for threatening academic freedom and censoring scientific research that might assist in the treatment of gender dysphoria.

There was also reportedly an academic petition signed by members of the relevant scientific community. For example, Lee Jussim, PhD., Chair of the Psychology Department at Rutgers University wrote, "If the Littman study is wrong, let someone produce evidence that it is wrong. Until that time, if the research p*sses some people off, who cares? Galileo and Darwin p*ssed people off too. Brown University should be ashamed of itself for caving to sociopolitical pressure. Science denial, anyone?" Similarly, Richard B. Krueger, MD (a Harvard Medical School graduate) of Columbia University College of Physicians and Surgeons, board certified psychiatrist specializing in the treatment of sexual disorders wrote, "Brown University's actions in its failure to support Dr. Littman's peer reviewed research are abhorrent." Similarly, Nicholas Wolfinger, PhD (UC Berkeley, UCLA), currently Professor of Family and Consumer Studies at the University of Utah wrote: "The well-being of trans youth and other sexual minorities is best served by more research, not less."

The onslaught of attacks resulted in the journal asking Dr. Littman to publish a "corrected" version of the paper. After careful review, the paper was again published with additional

information but no methodological nor data corrections—as no such errors were found. See https://www.psychologytoday.com/us/blog/rabble-rouser/201903/rapid-onset-gender-dysphoria. See also Littman, L., Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria, PLOS ONE March 19, 2019, https://doi.org/10.1371/journal.pone.0214157. Dr. Littman's paper was a key initial step in the alternative investigative hypothesis that the very recent and enormous increase in teenage girls seeking "gender transitioning" is due to a social contagion process at school, in peer groups, and on the internet. This theory has yet to be tested in detail.

71. UNDERLYING BIOLOGY IS NOT CHANGED BY ALTERING BODILY FEATURES TO "PASS" AS THE OPPOSITE SEX, NOR DO SUCH ALTERATIONS CHANGE DISEASE VULNERABILITIES ASSOCIATED WITH GENETICALLY-DEFINED SEX: Despite the increasing ability of hormones and various surgical procedures to reconfigure some male bodies to visually pass as female, or vice versa, the biology of the person remains as defined by genetic makeup, normatively by his (XY) or her (XX) chromosomes, including cellular, anatomic, and physiologic characteristics and the particular disease vulnerabilities associated with that chromosomally-defined sex. (See "Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences. Exploring the Biological Contributions to Human Health: Does Sex Matter?" Wizemann TM, Pardue ML, editors. Washington (DC): National Academies Press (US); 2001. PMID: 25057540.) For instance, the XX (genetically female) individual who takes testosterone to stimulate certain male secondary sex characteristics will nevertheless remain unable to produce sperm and father children. Contrary to assertions and hopes that medicine and society can fulfill the aspiration of the individual with sex-discordant

gender identity to become "a complete man" or "a complete woman," this is not biologically attainable. It is possible for some adolescents and adults to pass unnoticed as the opposite gender that they aspire to be—but with limitations, costs, and risks, as I detail later. See S. Levine (2018), Informed Consent for Transgendered Patients, J. of Sex & Marital Therapy, at 6, DOI: 10.1080/0092623X.2018.1518885 ("Informed Consent"); S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. Am. Acad Psychiatry Law 44, 236 at 238 ("Reflections").

72. ONE OF THE MOST CONTROVERSIAL AND CONTENTIOUS ISSUES IN TRANSGENDER SCIENCE IS THE RECENT EPIDEMIC OF ADOLESCENT FEMALE TO MALE GENDER DISCORDANT PATIENTS: How prevalent is the Sudden Onset Gender Dysphoria Epidemic in Teen Girls first described by the research of Dr. Littman at Brown University? In the UK, where centralized medical care provides data to track health care phenomenon, the number of adolescent girls seeking sex transitioning exploded *over 4,000% in the last decade.* Similarly, in the US, where we lack the same kinds of centralized health care data, it has been reported that in 2018 2% (2 in 100) of high school students identified on surveys as "transgender"—this is 200 times greater response— a 20,000% increase—over reports during past decades which showed a rate of only .01 percent (one in 10,000 people). See Johns MM, Lowry R, Andrzejewski J, et al. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students—19 States and Large Urban School Districts, 2017. MMWR Morb Mortal Wkly Rep 2019; 68:67–71.

Along with this increase in transgender patients and identifiers, has come *a radical and recent transformation of the patient population* from early onset males to rapid onset adolescent girls. Thus currently the majority of new patients with sex-gender discordance are not males with a long, stable history of gender dysphoria since early childhood—as they were for decades—but instead adolescent females with no documented long-term history of gender dysphoria—thus they experienced "rapid onset" transgender identification. Whole groups of female friends in colleges, high schools, and even middle schools across the country are reportedly coming out together in peer group clusters as "transgender." These are girls who — by detailed parental reports and self-reports—had never experienced any discomfort in their biological sex until they heard a coming-out story from a speaker at a school assembly or discovered the internet (YouTube) community of trans "influencer video stars."

This extraordinary change in new patient demographics appears more consistent with a theory of social contagion than of "immutable identification," "brain structures," "genetics," or other biological hypotheses. Many unsuspecting parents, whose children have never shown any signs for gender discordant feelings or ideas, are awakening to find their daughters in thrall to hip trans YouTube stars and "gender-affirming" educators and activist therapists who push life-changing interventions on these young girls—including double mastectomies and hormonal puberty blockers that can potentially cause permanent infertility. See Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2018 Aug 16;13(8):e0202330. doi: 10.1371/journal.pone.0202330. Erratum in: PLoS One. 2019 Mar 19;14(3):e0214157. PMID: 30114286; PMCID: PMC6095578.

73. GENERATING, CONSIDERING, AND TESTING ALTERNATIVE THEORIES PREVENTS CONFIRMATION BIAS. Several theories should be considered, as the science is currently unclear:

We should consider the genetics theory of transgender identity. But his theory cannot explain the rapid expansion of new GD cases (a 4,000% to 20,000% increase), as our genome is simply not changing that fast.

We should consider the "brain structures" theory of transgender identity. Yet there is only weak medical evidence to support this theory, and it cannot explain the rapid expansion of new gender dysphoria cases because brain structures are not changing that fast.

We should consider the theory that increased social acceptance of the transgender lifestyle is leading many people who were transgender all along to come out. Yet this theory fails to explain why *males and older women are not also coming out in the same huge numbers* and not coming out in "social peer group clusters," as adolescent females are reportedly doing.

We should consider the "immutable gender identity" theory. Yet this theory fails to explain the rapid expansion of patients. In addition, the "immutable" theory fails to explain the rapid expansion of "Rapid Onset Gender Dysphoria" reports—newly "trans" adolescent girl patients who reportedly showed no indication of gender dysphoria previously.

Having considered alternative theories—to avoid confirmation bias—it appears that another alternative theory might well be the most applicable, rational theory to explain the extreme, recent increases in the GD patient population: the Social Contagion hypothesis. Social contagion effects are also reportedly responsible for the massive, rapid increase in "recovered repressed memory" cases and also the extraordinary expansion of "multiple personality disorder"

cases in the 1990s. I also note the alternative investigative hypothesis that *social contagion effects would appear to be psychological/psychiatric problems and NOT physical medical problems requiring hormonal or surgical "treatments."*

74. ADOLESCENT FEMALE PSYCHOLOGY RESEARCH SHOWS WELL-DOCUMENTED PEER INFLUENCES on ANOREXIA, BULIMIA, DRUG ABUSE, and now GENDER DISCORDANT ("TRANSGENDER") SYMPTOMS. The Social Contagion theory for the large increase in reported Rapid Onset Gender Dysphoria in adolescent girls appears to be the most rational explanation for the reportedly dramatic (rapid, media related, hundreds of times increase, YouTube influenced, Peer Group influenced) explosion of gender discordant patients among adolescent female friend groups.

Adolescent female social contagion effects in psychiatric illness are well-known and well documented. Consider, for example, Bulimia and Anorexia — both of which spread rapidly in adolescent female friend groups. Se Allison S, Warin M, Bastiampillai T. Anorexia nervosa and social contagion: clinical implications. Aust N Z J Psychiatry. 2014 Feb;48(2):116-20. doi: 10.1177/0004867413502092. Epub 2013 Aug 22. PMID: 23969627.

It has been known for decades that adolescent females are highly prone to social contagion effects spreading psychiatric symptoms—e.g., Anorexia, Bulimia, Drug Abuse, etc.) are well known to be subject to "cluster" and "friendship" contagions as teens girls (and especially troubled teen girls) co-ruminate and share feelings at very high rates and with emotional depth. See, e.g., Crandall CS. Social contagion of binge eating. J Pers Soc Psychol. 1988 Oct;55(4):588-98. doi: 10.1037//0022-3514.55.4.588. PMID: 3193348.

For example, Prof. Amanda Rose at the University of Missouri has conducted research to understand why adolescent girls show such susceptibility to social contagion with psychiatric symptoms—"Teenage girls share symptoms via social contagions because their friendship processes involve "co-rumination," that is, taking on the emotional pain and concerns of their friends." See R. Schwatz-Mette and A. Rose, Co-Rumination Mediates Contagion of Internalizing Symptoms Within Youths' Friendships, Developmental Psychology 48(5):1355-65, February 2012, DOI: 10.1037/a0027484 Developmental Psychology, Vol. 48, No. 5, 1355–1365 0012-1649/12/$12.00 DOI: 10.1037/a0027484. This could be one explanation for why we are hearing increasing reports of" clusters" and "friend groups" of teen girls who are adopting a "transgender identity" and "transitioning" as friends together.

75. IDEOLOGICAL-POLITICAL PRESSURE SEEKS TO INSTITUTIONALIZE THE SYSTEMATIC NEGLIGENCE and METHODOLOGICAL ERROR OF CONFIRMATION BIAS: Because of the efforts of ill-informed legal and medical professionals and the intense activity of political trans activists— health providers (in many fields) are now NOT permitted to openly asks questions, properly investigate alternative diagnoses, or explore alternative hypotheses for the symptoms of gender dysphoria patients. They are compelled (sometimes under fear of employment termination or legal attacks) to adopt a patient's self-diagnosis and only support "transgender affirming" medical interventions. These providers are thus being pressured and/or compelled to commit the scientific and medical malpractice of Confirmation Bias. (See detailed discussion above on confirmation bias.) Unexamined "affirming" medical interventions—based on uncorroborated patient self-reports, assessed by mental health professionals with no methodology for discerning true from false patient reports, with no ability to decipher accurate from contaminated "memories," with no alternative treatments offered, and no alternative explanations

(e.g., social contagion) explored—are medical, psychological, surgical, and endocrinological negligence and a violation of the most basic, essential scientific and medical practices and methods requiring the generation and testing of alternative hypotheses. In sum, the industry actually requires "confirmation bias"—one of the most serious of all methodological diagnostic failures. See e.g. Mendel, R. et. al., Confirmation bias: why psychiatrists stick to wrong preliminary diagnoses, Psychological Medicine, Oxford University Press, 20 May 2011 ("Diagnostic errors can have tremendous consequences because they can result in a fatal chain of wrong decisions. Experts assume that physicians' desire to confirm a preliminary diagnosis while failing to seek contradictory evidence is an important reason for wrong diagnoses. This tendency is called 'confirmation bias."); see also, Doherty, T.S. and Carroll, A.E., Believing in Overcoming Cognitive Biases, American Medical Association Journal of Ethics, 2020;22(9):E773-778 ("Like all humans, health professionals are subject to cognitive biases that can render diagnoses and treatment decisions vulnerable to error. Learning effective debiasing strategies and cultivating awareness of confirmation, anchoring, and outcomes biases and the affect heuristic, among others, and their effects on clinical decision making should be prioritized in all stages of medical education…. Confirmation bias is the selective gathering and interpretation of evidence consistent with current beliefs and the neglect of evidence that contradicts them."); see also, Hershberger PJ, Part HM, Markert RJ, Cohen SM, Finger WW. Teaching awareness of cognitive bias in medical decision making. *Acad Med*. 1995;70(8):661.

76. GIVEN THE LACK OF RESEARCH, IT IS RECKLESS TO PERMIT CHILDREN TO SELF-DIAGNOSE WHEN THE "TREATMENTS" WILL PRODUCE LIFE-LONG STERILIZATION and/or OTHER PERMANANT INJURIES TO NORMAL, HEALTHY ORGANS: In some jurisdictions in America now child or adolescent patients can—without parental

permission or even parental notification—receive hormones to begin the experimental treatment of "transitioning" with no competent diagnostic investigation or professional assessment of gender dysphoria and no competent medical investigation, testing, or consideration of alternative hypotheses. Worst of all, providers can be coerced by law, collegial pressures, or "cancel culture" ideology to comply with the troubled child's/teen's/patient's amateur self-diagnosis or be faced with potentially career ending allegations of "conversion therapy." Politically tainted, pseudo-science, experimental, unproven medical practices have caused grave harm to millions in the past. (See the discussion of lobotomies, repressed memory therapy, multiple personality therapy, rebirthing therapy, etc. above.) Unethical, politically driven, experimental medical errors should not be repeated today.

77. EXPERIMENTATION on SEX-GENDER DISCORDANT PATIENTS IS ESPECIALLY LIKELY TO CAUSE HARM TO MINORITY PATIENTS FROM HISTORICALLY MARGINALIZED COMMUNITIES. The development of effective strategies to impact long-term physical and psychological health in patients who experience sex-discordant gender identity should be undertaken with recognition of the disproportionate burden of this condition in a number of vulnerable minority populations of children. These include:

- children with a prior history of psychiatric illness (See, e.g., Kaltiala-Heino, R., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child and adolescent psychiatry and mental health*, *9*, 9. https://doi.org/10.1186/s13034-015-0042-y

- children of color (See, e.g., G. Rider et al. (2018), Health and Care Utilization of Transgender/Gender Non-Conforming Youth: A Population Based Study, Pediatrics at 4, DOI: 10.1542/peds.2017-1683.
- children with mental developmental disabilities (See, e.g., Bedard, C., Zhang, H.L. & Zucker, K.J. Gender Identity and Sexual Orientation in People with Developmental Disabilities. *Sex Disabil* 28**,** 165–175 (2010). https://doi.org/10.1007/s11195-010-9155-7
- children on the autistic spectrum (See, e.g., de Vries, A. L., Noens, I. L., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A. & Doreleijers, T. A. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord* 40, 930-936, doi:10.1007/s10803-010-0935-9 (2010).
- children residing in foster care homes and adopted children (See, e.g., See e.g., D. Shumer et al. (2017), Overrepresentation of Adopted Adolescents at a Hospital-Based Gender Dysphoria Clinic, Transgender Health Vol. 2(1).

78. "GENDER AFFIRMATIVE" TREATMENTS DAMAGE or DESTROY HEALTHY BODILY ORGANS, LEADING TO LOSS OF ESSENTIAL BODILY FUNCTIONS (e.g. Medically Induced Sterilization): Despite the fact that gender dysphoria represents a psychological condition (as catalogued in the DSM since the third edition of this publication), some conceptualize the condition as a medical illness similar to cancer. When considered from this viewpoint, the goal of "treatment" is to alter the appearance of the body to conform to a patient's perceived sexual identity, including the physical removal of unwanted "diseased" sexual organs. Since undesired body parts are fully formed and functional prior to hormonal or surgical intervention, the

result of these "therapies" is injury to innate sexual ability. In particular, loss or alteration of primary sexual organs leads directly to impairment of reproductive potential. Recognition of this obvious consequence is the basis for the development of new arenas of medical practice where there is an attempt to restore what has been intentionally destroyed. See, e.g., Ainsworth AJ, Allyse M, Khan Z. Fertility Preservation for Transgender Individuals: A Review. Mayo Clin Proc. 2020 Apr; 95(4):784-792. doi: 10.1016/j.mayocp.2019.10.040. Epub 2020 Feb 27. PMID: 32115195. As correctly noted by Dr. Levine, gender dysphoria is unique in that it is "the only psychiatric condition to be treated by surgery, even though no endocrine or surgical intervention package corrects any identified biological abnormality." See, e.g., S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. American Academy of Psychiatry and Law, 44, 236 at 238 ("Reflections"), at 240.)

79. A DEVELOPMENTAL MODEL PROVIDES ALTERNATIVE HYPOTHESES TO THE UNEXAMINED "AFFIRMATON" MODEL: The diagnosis of "gender dysphoria" encompasses a diverse array of conditions. While the etiologic contributors to sex discordant gender identity remain to be fully identified and characterized, differences both in kind and degree within individuals and across varied populations creates challenges in establishing specific approaches to alleviate associated suffering. For example, data from adults cannot be assumed to apply equally to children. Nor can data from children who present with sex discordant gender pre-pubertally be presumed to apply to the growing number of post-pubertal adolescent females presenting with this condition.

80. NO COMPETENT, SCIENTIFICALLY VALID and RELIABLE COST-BENEFIT ANALYSIS HAS BEEN DONE ON "GENDER AFFIRMATIVE" TREATMENTS. When the FDA tests a drug, the safety analysis looks at all related risks. Specifically, the drug must not

only be effective, but it must not cause side effects that are more damaging than the proposed treatment. This is one of the gender transition industry's key weaknesses. Not only have the "treatments" *not* been proven reliably effective compared to *no* treatment, they are designed with existing knowledge of well-documented, long-term health problems and damages (e.g., testosterone use by transgender men increases the risk of fatal heart disease, estrogen use by transgender women increases risk of blood clots and strokes, gender transition industry treatments—if completed—can cause life-long sterility, etc.).

81. LACK OF INTEGRATION OF CARE BY PROVIDERS IN THE GENDER TRANSITION INDUSTRY INCREASES DANGERS TO PATIENTS: It is too often the case in the gender transition industry that "nobody is in charge" of a patient's care. The mental health professionals know little about the risks of surgery and the surgeons know little about the defects in mental health methodologies and the endocrinologists are only following the hormonal treatments and many are not aware of the serious methodological research defects in this field. Such disjointed care can increase dangers to patients. On cases showing such a lack of integration and uncertain chain of command, reliable measurements of the divergent, multi-disciplinary risks to patients of these treatments (e.g. hormones, incomplete therapy, or surgical side effects) are precluded and too often ignored. The plaintiffs' expert witness reports in this case appear to ignore this issue.

82. SUMMARY OPINIONS:

- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are helped by such procedures.

- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are injured or harmed by such procedures.
- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting the reliability and validity of assessing gender identity by relying solely upon the expressed desires of a patient.
- There are no long-term, peer-reviewed published, reliable and valid, research studies documenting any valid and reliable biological, medical, surgical, radiological, psychological, or other objective assessment of gender identity or gender dysphoria.
- A currently unknown percentage and number of patients reporting gender dysphoria suffer from mental illness(es) that complicate and may distort their judgments and perceptions of gender identity.
- A currently unknown percentage and number of patients reporting gender dysphoria are being manipulated by a—peer group, social media, YouTube role modeling, and/or parental—social contagion and social pressure processes.
- Patients suffering from gender dysphoria or related issues have a right to be protected from experimental, potentially harmful treatments lacking reliable and valid, peer reviewed, published, long-term scientific evidence of safety and effectiveness.
- It would be a serious violation of licensing rules, ethical rules, and professional standards of care for a health care professional to provide gender transition or related procedures to any patient without first properly obtaining informed consent

including informing the patient and/or guardian(s) of the lack of valid and reliable on the long-term risks and benefits of "affirmation" treatments.

- A large percentage of children (over 80% in some studies) who questioned their gender identity will, if left alone, develop an acceptance of their natal (biological) sex.
- Medical treatments may differ significantly by sex according to chromosomal assessment but not gender identity. Misinforming physicians of a patient's biological sex can have deleterious effects on treatment for medical conditions.
- Affirmation medical treatments—hormones and surgery—for gender dysphoria and "transitioning" have not been accepted by the relevant scientific communities (biology, genetics, neonatolgy, medicine, psychology, etc).
- Gender transition "affirmation" medical assessments and treatments—hormones and surgery—for gender dysphoria and "transitioning" have no known, peer reviewed and published error rates—the treatments and assessment methods lack demonstrated, reliable and valid error rates.
- Political activists, political activist physicians, and politically active medical organizations that operate by voting methodologies (e.g, WPATH, the American Medical Association, the American Academy of Pediatrics, the American Endocrine Society) are not the relevant scientific community, they are politically active professional organizations. These organizations operate via consensus-seeking methodology (voting) and political ideologies rather than evidence-based scientific methodologies.

- Experts in legal cases have an ethical obligation to honestly, fairly, and accurately discuss the international controversy regarding the safety, effectiveness, reliability, and credibility of the gender transition industry.
- With the limited and poor quality data currently available on the purported efficacy of blocking normally timed puberty, administering of cross-sex hormones and gender affirming surgeries in alleviating psychological morbidity for youth who experience sex-discordant gender identity and the associated serious medical risks associated with these interventions, it cannot be concluded that this approach is "medically necessary."

83. LIMITATIONS ON EXPERT REPORTS: My opinions and hypotheses in this matter are—as all expert reports—subject to the limitations of documentary and related evidence, the impossibility of absolute predictions, as well as the limitations of social, biological, and medical science. I have not met with, nor personally interviewed, anyone in this case. As always, I have no expert opinions regarding the veracity of witnesses in this case. I have not yet reviewed all of the evidence in this case and my opinions are subject to change at any time as new information becomes available to me. Only the trier of fact can determine the credibility of witnesses and how scientific research may or may not be related to the specific facts of any particular case. In my opinion, a key role of an expert witness is to help the court, lawyers, parties, and the public understand and apply reliable scientific, technical, and investigative principles, hypotheses, methods, and information.

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

Executed on May 1, 2022.

Paul W. Hruz, M.D., Ph.D.

Curriculum Vitae

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Education

1987	BS, Chemistry, Marquette University, Milwaukee, WI
1993	PhD, Biochemistry, Medical College of Wisconsin, Milwaukee, WI Elucidation of Structural, Mechanistic, and Regulatory Elements in 3-Hydroxy-3-Methlyglutaryl-Coenzyme A Lyase, Henry Miziorko
1994	MD, Medicine, Medical College of Wisconsin, Milwaukee, WI
1994 - 1997	Pediatric Residency, University of Washington, Seattle, Washington
1997 - 2000	Pediatric Endocrinology Fellowship, Washington University, Saint Louis, MO
2017	Certification in Healthcare Ethics, National Catholic Bioethics Center, Philadelphia, PA

Academic Positions / Employment

1996 - 1997	Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA
2000 - 2003	Instructor in Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2003 - 2011	Assistant Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO
2004 - 2011	Assistant Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO
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Clinical Title and Responsibilities

	General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per yr, St. Louis Children's Hosptial
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital
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Teaching Title and Responsibilities

2009 - Pres	Lecturer, Markey Course-Diabetes Module
2020 - 2020	Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine

University, School of Medicine and Hospital Appointments and Committees

University

2012 - 2020	Disorders of Sexual Development Multidisciplinary Care Program

School of Medicine

2013 - 2020	Molecular Cell Biology Graduate Student Admissions Committee
2014 - Pres	Research Consultant, ICTS Research Forum - Child Health

Hospital

2000 - Pres	Attending Physician, St. Louis Children's Hospital

Medical Licensure and Certifications

1997 - Pres	Board Certified in General Pediatrics
2000 - Pres	MO Stae License #2000155004
2001 - Pres	Board Certified in Pediatric Endocrinology & Metabolism

Honors and Awards

1987	National Institute of Chemists Research and Recognition Award
1987	Phi Beta Kappa
1987	Phi Lambda Upsilon (Honorary Chemical Society)
1988	American Heart Association Predoctoral Fellowship Award
1994	Alpha Omega Alpha
1994	Armond J. Quick Award for Excellence in Biochemistry

1994	NIDDK/Diabetes Branch Most Outstanding Resident
1998	Pfizer Postdoctoral Fellowship Award
2002	Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University
2013	Julio V Santiago, M.D. Scholar in Pediatrics
2017	Redemptor Hominis Award for Outstanding Contributions to the Study of Bioethics
2018	Eli Lilly Outstanding Contribution to Drug Discovery: Emerging Biology Award
2018	Scholar-Innovator Award, Harrington Discovery Institute
2021	Linacre Award

Editorial Responsibilities

Editorial Ad Hoc Reviews

AIDS
AIDS Research and Human Retroviruses
American Journal of Pathology
American Journal of Physiology
British Journal of Pharmacology
Circulation Research
Clinical Pharmacology & Therapeutics
Comparative Biochemistry and Physiology
Diabetes
Experimental Biology and Medicine
Future Virology
Journal of Antimicrobial Chemotherapy
Journal of Clinical Endocrinology & Metabolism
Journal of Molecular and Cellular Cardiology
Obesity Research

2000 - Pres	Journal of Biological Chemistry
2013 - Pres	PlosOne
2016 - Pres	Scientific Reports
2018 - Pres	Nutrients

Editorial Boards

2014 - 2015	Endocrinology and Metabolism Clinics of North America

National Panels, Committees

2017 - Pres	Consultant, Catholic Health Association
2021 - Pres	Consulting Fellow, National Catholic Bioethics Center

National Boards

2020 - Pres	WU ICTS Clinical and Translational Research Funding Program (CTRFP) Review Committee

Community Service Contributions

Professional Societies and Organizations

1992 - 2004	American Medical Association
1994 - 2005	American Academy of Pediatrics
1995 - 2014	American Association for the Advancement of Science
1998 - Pres	American Diabetes Association
1998 - Pres	Endocrine Society
1999 - Pres	Pediatric Endocrine Society
2004 - 2007	American Chemical Society
2004 - 2018	American Society for Biochemistry and Molecular Biology
2004 - 2020	Society for Pediatric Research
2005 - 2020	Full Fellow of the American Academy of Pediatrics
2013 - Pres	International Society for Pediatric and Adolescent Diabetes
2018 - Pres	American College of Pediatricians

Major Invited Professorships and Lectures

2002	Pediatric Grand Rounds, St. Louis Children's Hospital, St Louis, MO
2004	National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA
2004	NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD
2005	Endocrine Grand Rounds, University of Indiana, Indianapolis, IN
2005	The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA
2006	Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ
2007	American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL
2007	Minority Access to Research Careers Seminar, University of Arizona, Tucson, AZ
2007	MSTP Annual Visiting Alumnus Lecture, Medical College of Wisconsin , Milwaukee, WI
2007	Pediatric Grand Rounds, St Louis Children’s Hospital, St Louis, MO
2008	Division of Endocrinology, Diabetes and Nutrition Grand Rounds, Boston University, Boston, MA
2009	Pediatric Grand Rounds, St Louis Children's Hospital, St. Louis, MO
2010	American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL
2010	School of Biological Sciences Conference Series, University of Missouri Kansas City, Kansas City, MO
2011	Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb,, Chicago, IL
2013	Pediatric Grand Rounds, St Louis Children's Hospital, ST LOUIS, MO
2013	Clinical Practice Update Lecture, St Louis Children's Hospital, St Louis, MO
2014	Pediatric Academic Societies Meeting,, Vancouver, Canada
2014	American Diabetes Association 74th Scientific Sessions, , San Francisco, CA
2017	Division of Pediatric Endocrinology Metabolism Rounds, University of Michigan, Ann Arbor, MI

2017 Catholic Medical Association National Conference, Denver, CO

2018 Obstetrics, Gynecology & Women's Health Grand Rounds, Saint Louis University, St. Louis, MO

2018 Medical Grand Rounds, Sindicato Médico del Uruguay, Montevideo, Uraquay

2018 Internal Medicine Grand Rounds, Texas Tech , Lubbock, TX

2019 Veritas Center for Ethics in Public Life Conference, Franciscan University, Steubenville, OH

2019 MaterCare International Conference, Rome, Italy

2019 Child Health Policy Forum, Notre Dame University, South Bend , IN

2021 Obstetrics & Gynecology Grand Rounds, University of Tennessee, Knoxville , TN

Consulting Relationships and Board Memberships

1996 - 2012 Consultant, Bristol Myers Squibb

1997 - 2012 Consultant, Gilead Sciences

Research Support

Completed Governmental Support

2001 - 2006 K-08 A149747, NIH
Mechanism of GLUT4 Inhibition by HIV Protease Inhibitors
Role: Principal Investigator

2007 - 2012 R01
Mechanisms for Altered Glucose Homeostasis During HAART
Role: Principal Investigator
Total cost: $800,000.00

2009 - 2011 R01 Student Supp
Mechanisms for Altered Glucose Homeostasis During HAART
Role: Principal Investigator
Total cost: $25,128.00

2009 - 2014 R01
Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis
Role: Principal Investigator
Total cost: $1,250,000.00

2017 - 2019 R-21 1R21AI130584 , National Institutes of Health
SELECTIVE INHIBITION OF THE P. FALCIPARUM GLUCOSE TRANSPORTER PFHT
Role: Principal Investigator
Total cost: $228,750.00

Completed Non-Governmental Support

2015 Novel HIV Protease Inhibitors and GLUT4
Role: Principal Investigator

2008 - 2011 II
Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure
Role: Co-Investigator
PI: Hruz
Total cost: $249,999.00

2009 - 2012 Research Program
Regulation of GLUT4 Intrinsic Activity
Role: Principal Investigator
Total cost: $268,262.00

2010 - 2011 Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function
Role: Principal Investigator

2012 - 2015 II
Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins
Role: Principal Investigator
Total cost: $375,000.00

2017 - 2020 Prevention And Treatment Of Hepatic Steatosis Through Selective Targeting Of GLUT8
Role: Co-Principal Investigator
PI: DeBosch
Total cost: $450,000.00

2017 - 2021 Matching Micro Grant
Novel Treatment of Fatty Liver Disease (CDD/LEAP)
Role: Principal Investigator
Total cost: $68,500.00

2018 - 2021 LEAP Innovator Challenge
Novel Treatment of Fatty Liver Disease
Role: Principal Investigator
Total cost: $68,500.00

2019 - 2021 Scholar-Innovator Award HDI2019-SI-4555 , Harrington Foundation
Novel Treatment of Non-Alcoholic Fatty Liver Disease
Role: Principal Investigator
Total cost: $379,000.00

Current Governmental Support

2021 - 2025 R-01 DK126622 (Co-investigator), 8/25/2021-7/31/2025, NIH-NIDDK, , NIH
Leveraging glucose transport and the adaptive fasting response to modulate hepatic metabolism
Role: Co-Investigator
PI: DeBosch

Pending Non-Governmental Support

2015 Novel HIV Protease Inhibitors and GLUT4
Role: Principal Investigator

Trainee/Mentee/Sponsorship Record

Current Trainees

2019 Ava Suda, Other, Pre-med

Past Trainees

2002 - 2002 Nishant Raj- Undergraduate Student, Other
Study area: Researcher

2002 - 2010 Joseph Koster, PhD, Postdoctoral Fellow
Study area: Researcher

2003 - 2004 Johann Hertel, Medical Student
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 - 2003 John Paul Shen, Medical Student
Study area: Research

2004 - 2005 Carl Cassel- High School Student, Other
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student, Other
Study area: Researcher

2004 - 2004 Kaiming Wu- High School Student, Other
Study area: Research

2005 - 2005 Helena Johnson, Graduate Student

2005 - 2005 Jeremy Etzkorn, Medical Student
Study area: Researcher

2005 - 2005 Dominic Doran, DSc, Postdoctoral Fellow
Study area: HIV Protease Inhibitor Effects on Exercize Tolerance

2006 - 2006 Ramon Jin, Graduate Student
Study area: Research

2006 - 2006 Taekyung Kim, Graduate Student
Study area: Research

2007 - 2007 Jan Freiss- Undergraduate Student, Other
Study area: Researcher

2007 - 2008 Kai-Chien Yang, Graduate Student
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 - 2007 Paul Buske, Graduate Student
Study area: Research

2007 - 2007 Randy Colvin, Medical Student
Study area: Researcher

2008 - 2011 Arpita Vyas, MD, Clinical Fellow
Study area: Research
Present position: Assistant Professor, Michigan State University, Lansing MI

2008 - 2009 Candace Reno, Graduate Student
Study area: Research
Present position: Research Associate, University of Utah

2008 - 2012 Dennis Woo- Undergraduate Student, Other
Study area: Researcher
Present position: MSTP Student, USC, Los Angeles CA

2008 - 2008 Temitope Aiyejorun, Graduate Student
Study area: Research

2009 - 2009 Anne-Sophie Stolle- Undergraduate Student, Other
Study area: Research

2009 - 2009 Matthew Hruz- High School Student, Other
Study area: Research
Present position: Computer Programmer, Consumer Affairs, Tulsa OK

2009 - 2009 Stephanie Scherer, Graduate Student
Study area: Research

2010 - 2014 Lauren Flessner, PhD, Postdoctoral Fellow
Present position: Instructor, Syracuse University

2010 - 2010 Constance Haufe- Undergraduate Student, Other
Study area: Researcher

2010 - 2011 Corinna Wilde- Undergraduate Student, Other
Study area: Researcher

2010 - 2010 Samuel Lite- High School Student, Other
Study area: Research

2011 - 2016 Thomas Kraft, Graduate Student
Study area: Glucose transporter structure/function
Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

2011 - 2011 Amanda Koenig- High School Student, Other
Study area: Research

2011 - 2012 Lisa Becker- Undergraduate Student, Other

2011 - 2011 Melissa Al-Jaoude- High School Students, Other

2014 - 2014 David Hannibal, Clinical Research Trainee

Bibliography

A. Journal Articles

1. Hruz PW, Narasimhan C, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase: affinity labeling of the Pseudomonas mevalonii enzyme and assignment of cysteine-237 to the active site. *Biochemistry*. 1992;31(29):6842-7. PMID:1637819
2. Hruz PW, Miziorko HM. Avian 3-hydroxy-3-methylglutaryl-CoA lyase: sensitivity of enzyme activity to thiol/disulfide exchange and identification of proximal reactive cysteines. *Protein Sci*. 1992;1(9):1144-53. doi:10.1002/pro.5560010908 PMCID:PMC2142181 PMID:1304393
3. Mitchell GA, Robert MF, Hruz PW, Wang S, Fontaine G, Behnke CE, Mende-Mueller LM, Schappert K, Lee C, Gibson KM, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*. 1993;268(6):4376-81. PMID:8440722
4. Hruz PW, Anderson VE, Miziorko HM. 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*. 1993;1162(1-2):149-54. PMID:8095409
5. Roberts JR, Narasimhan C, Hruz PW, Mitchell GA, Miziorko HM. 3-Hydroxy-3-methylglutaryl-CoA lyase: expression and isolation of the recombinant human enzyme and investigation of a mechanism for regulation of enzyme activity. *J Biol Chem*. 1994;269(27):17841-6. PMID:8027038
6. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 7 of the GLUT1 glucose transporter. *J Biol Chem*. 1999;274(51):36176-80. PMID:10593902
7. Murata H, Hruz PW, Mueckler M. The mechanism of insulin resistance caused by HIV protease inhibitor therapy. *J Biol Chem*. 2000;275(27):20251-4. doi:10.1074/jbc.C000228200 PMID:10806189
8. Hruz PW, Mueckler MM. Cysteine-scanning mutagenesis of transmembrane segment 11 of the GLUT1 facilitative glucose transporter. *Biochemistry*. 2000;39(31):9367-72. PMID:10924131
9. Hruz PW, Mueckler MM. Structural analysis of the GLUT1 facilitative glucose transporter (review). *Mol Membr Biol*. 2001;18(3):183-93. PMID:11681785

10. Murata H, Hruz PW, Mueckler M. Investigating the cellular targets of HIV protease inhibitors: implications for metabolic disorders and improvements in drug therapy. *Curr Drug Targets Infect Disord*. 2002;2(1):1-8. PMID:12462148
11. Hruz PW, Murata H, Qiu H, Mueckler M. Indinavir induces acute and reversible peripheral insulin resistance in rats. *Diabetes*. 2002;51(4):937-42. PMID:11916910
12. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*. 2002;16(6):859-63. PMID:11919487
13. Koster JC, Remedi MS, Qiu H, Nichols CG, Hruz PW. HIV protease inhibitors acutely impair glucose-stimulated insulin release. *Diabetes*. 2003;52(7):1695-700. PMCID:PMC1403824 PMID:12829635
14. Liao Y, Shikapwashya ON, Shteyer E, Dieckgraefe BK, Hruz PW, Rudnick DA. Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. *J Biol Chem*. 2004;279(41):43107-16. doi:10.1074/jbc.M407969200 PMID:15265859
15. Shteyer E, Liao Y, Muglia LJ, Hruz PW, Rudnick DA. Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. *Hepatology*. 2004;40(6):1322-32. doi:10.1002/hep.20462 PMID:15565660
16. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem*. 2004;279(53):55147-52. doi:10.1074/jbc.M410826200 PMCID:PMC1403823 PMID:15496402
17. Yan Q, Hruz PW. Direct comparison of the acute in vivo effects of HIV protease inhibitors on peripheral glucose disposal. *J Acquir Immune Defic Syndr*. 2005;40(4):398-403. PMCID:PMC1360159 PMID:16280693
18. Hruz PW. Molecular Mechanisms for Altered Glucose Homeostasis in HIV Infection. *Am J Infect Dis*. 2006;2(3):187-192. PMCID:PMC1716153 PMID:17186064
19. Turmelle YP, Shikapwashya O, Tu S, Hruz PW, Yan Q, Rudnick DA. Rosiglitazone inhibits mouse liver regeneration. *FASEB J*. 2006;20(14):2609-11. doi:10.1096/fj.06-6511fje PMID:17077279
20. Hruz PW, Yan Q, Struthers H, Jay PY. HIV protease inhibitors that block GLUT4 precipitate acute, decompensated heart failure in a mouse model of dilated cardiomyopathy. *FASEB J*. 2008;22(7):2161-7. doi:10.1096/fj.07-102269 PMID:18256305
21. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. doi:10.1097/COH.0b013e3283139134 PMCID:PMC2680222 PMID:19373039
22. Flint OP, Noor MA, Hruz PW, Hylemon PB, Yarasheski K, Kotler DP, Parker RA, Bellamine A. The role of protease inhibitors in the pathogenesis of HIV-associated lipodystrophy: cellular mechanisms and clinical implications. *Toxicol Pathol*. 2009;37(1):65-77. doi:10.1177/0192623308327119 PMCID:PMC3170409 PMID:19171928
23. Tu P, Bhasin S, Hruz PW, Herbst KL, Castellani LW, Hua N, Hamilton JA, Guo W. Genetic disruption of myostatin reduces the development of proatherogenic dyslipidemia and atherogenic lesions in Ldlr null mice. *Diabetes*. 2009;58(8):1739-48. doi:10.2337/db09-0349 PMCID:PMC2712781 PMID:19509018
24. Guo W, Wong S, Pudney J, Jasuja R, Hua N, Jiang L, Miller A, Hruz PW, Hamilton JA, Bhasin S. Acipimox, an inhibitor of lipolysis, attenuates atherogenesis in LDLR-null mice treated with HIV protease inhibitor ritonavir. *Arterioscler Thromb Vasc Biol*. 2009;29(12):2028-32. doi:10.1161/ATVBAHA.109.191304 PMCID:PMC2783673 PMID:19762785
25. Vyas AK, Koster JC, Tzekov A, Hruz PW. Effects of the HIV protease inhibitor ritonavir on GLUT4 knock-out mice. *J Biol Chem*. 2010;285(47):36395-400. doi:10.1074/jbc.M110.176321 PMCID:PMC2978568 PMID:20864532

26. Gazit V, Weymann A, Hartman E, Finck BN, Hruz PW, Tzekov A, Rudnick DA. Liver regeneration is impaired in lipodystrophic fatty liver dystrophy mice. *Hepatology*. 2010;52(6):2109-17. doi:10.1002/hep.23920 PMCID:PMC2991544 PMID:20967828
27. Hresko RC, Hruz PW. HIV protease inhibitors act as competitive inhibitors of the cytoplasmic glucose binding site of GLUTs with differing affinities for GLUT1 and GLUT4. *PLoS One*. 2011;6(9):e25237. doi:10.1371/journal.pone.0025237 PMCID:PMC3179492 PMID:21966466
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36. Kraft TE, Armstrong C, Heitmeier MR, Odom AR, Hruz PW. The Glucose Transporter PfHT1 Is an Antimalarial Target of the HIV Protease Inhibitor Lopinavir. *Antimicrob Agents Chemother*. 2015;59(10):6203-9. doi:10.1128/AAC.00899-15 PMCID:PMC4576095 PMID:26248369
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39. Kraft TE, Heitmeier MR, Putanko M, Edwards RL, Ilagan MX, Payne MA, Autry JM, Thomas DD, Odom AR, Hruz PW. A Novel Fluorescence Resonance Energy Transfer-Based Screen in High-Throughput Format To Identify Inhibitors of Malarial and Human Glucose Transporters. *Antimicrob Agents Chemother*. 2016;60(12):7407-7414. PMCID:PMC5119023 PMID:27736766

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41. Edwards RL, Brothers RC, Wang X, Maron MI, Ziniel PD, Tsang PS, Kraft TE, Hruz PW, Williamson KC, Dowd CS, John ARO. MEPicides: potent antimalarial prodrugs targeting isoprenoid biosynthesis. *Sci Rep*. 2017;7(1):8400. PMCID:PMC5567135 PMID:28827774
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43. Wei C, Heitmeier M, Hruz PW, Shanmugam M. Evaluating the Efficacy of GLUT Inhibitors Using a Seahorse Extracellular Flux Analyzer. *Methods Mol Biol*. 2018;1713:69-75. PMID:29218518
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49. Zhang Y, Shaikh N, Ferey JL, Wankhade UD, Chintapalli SV, Higgins CB, Crowley JR, Heitmeier MR, Stothard AI, Mihi B, Good M, Higashiyama T, Swarts BM, Hruz PW, Shankar K, Tarr PI, DeBosch BJ. Lactotrehalose, an Analog of Trehalose, Increases Energy Metabolism Without Promoting Clostridioides difficile Infection in Mice. *Gastroenterology*. 2020;158(5):1402-1416.e2. PMCID:PMC7103499 PMID:31838076
50. Malone WJ, Hruz PW, Mason JW, Beck S. Letter to the Editor from William J. Malone: "Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective". *J Clin Endocrinol Metab*. 2021. PMID:33772300

C2. Chapters

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB. Endocrine Disorders in HIV/AIDS. In: *The Washington Manual Endocrinology Subspecialty Consult* Philadelphia, PA; 2008:321-328.
2. Paul W Hruz. Medical Approaches to Alleviating Gender Dysphoria In: Edward J Furton, eds. *Transgender Issues in Catholic Health Care* Philadelphia PA; 2021:1-42.

C4. Invited Publications

1. Grunfeld C, Kotler DP, Arnett DK, Falutz JM, Haffner SM, Hruz P, Masur H, Meigs JB, Mulligan K, Reiss P, Samaras K, Working Group 1. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*. 2008;118(2):e20-8. PMCID: PMC3170411 PMID: 18566314
2. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. PMCID: PMC2680222 PMID: 19373039
3. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459-68. PMCID: PMC3115529 PMID: 21663839
4. Hruz PW. HIV and endocrine disorders. *Endocrinol Metab Clin North Am*. 2014;43(3): xvii–xviii. PMID: 25169571
5. Hruz PW. Commentary. *Clin Chem*. 2015;61(12):1444. PMID: 26614228
6. Hruz PW, Mayer LS, and McHugh PR. Growing Pains: Problems with Pubertal Suppression in Treating Gender Dysphoria *The New Atlantis*. 2017;52:3-36.
7. Hruz, PW. The Use of Cross-Sex Steroids in Treating Gender Dysphoria *Natl Cathol Bioeth Q*. 2018;17(4):1-11.
8. Hruz, PW. Experimental Approaches to Alleviating Gender Dysphoria in Children *Nat Cathol Bioeth Q*. 2019;19(1):89-104.

Clinician Educator Portfolio

CLINICAL CONTRIBUTIONS

Summaries of ongoing clinical activities

	General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per yr, St. Louis Children's Hosptial
2000 - Pres	Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital
2000 - Pres	Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 50 patient visits per month, St. Louis Children's Hospital

EDUCATIONAL CONTRIBUTIONS

Direct teaching

Classroom

2009 - Pres	Lecturer, Markey Course-Diabetes Module
2020 - 2020	Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine

Clinical

2000 - Pres	Lecturer, Medical Student Growth Lecture (Women and Children's Health Rotation): Variable
2000 - Pres	Lecturer, Pediatric Endocrinology Journal Club: Presentations yearly
2009 - Pres	Facilitator, Medical Student Endocrinology and Metabolism Course, Small group
2016 - Pres	Facilitator, Medical Student Endocrinology and Metabolism Course, Small group

Other

	Facilitator, Cell Biology Graduate Student Journal Club, 4 hour/year
	Facilitator, Discussion: Pituitary, Growth & Gonadal Cases, 2 hours/year
2000 - Pres	Lecturer, Metabolism Clinical Rounds/Research Seminar: Presentations twice yearly
2009 - Pres	Facilitator, Biology 5011- Ethics and Research Science, 6 hours/year
2016 - Pres	Lecturer, Cell Signaling Course, Diabetes module, 3 hours/year

ANNUAL SUMMARIES

OTHER

Participated in research studies

Pres	Development of Novel Small Molecule Hexose Transport Inhibitors for Glucose-Dependent Disesases Paul W Hruz.

DOC. 69-6

DEFENDANT'S EXHIBIT 6

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF PATRICK HUNTER

My name is Patrick Hunter MD. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein. My CV is attached to this declaration.

In the past four years, I have not provided expert testimony in any case.

I am compensated the rate of $ 450 per hour for my work on this matter. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

1. I submit this expert declaration based upon my personal knowledge, my experience as a pediatrician with an advanced degree in bioethics, and my review of the literature discussed below.
2. If called to testify in this matter, I would testify truthfully based on my expert opinion.

I. Qualifications and Experience

3. I am a pediatrician with a master's degree in bioethics. I received my medical degree from the University of Louisville School of Medicine in 1992 and completed a pediatric residency at Tripler Army Medical Center in 1995. I obtained board certification in general pediatrics in 1995 and have continuously maintained that certification. I obtained a Master of Science degree in bioethics from the University of Mary in 2020. I have served on the ethics committee at Nemours Children Hospital, Orlando.
4. At Scotland Memorial Hospital, I served as pediatric department chair, medical executive committee chair, chief of the medical staff, and on the physician effectiveness committee. This physician effectiveness committee addressed physician professionalism and ethics. I also served on this hospital's governing board and operating committee.
5. I have held teaching positions at the rank of clinical and associate professors at the University of Hawaii and the Uniformed Services University of the Health Sciences. I currently hold academic positions at the University of Central Florida and Florida State University. I have taught pediatrics and bioethics to medical students and resident physicians at Tripler Army Medical Center, the University of Central Florida, and Nemours Children's Hospital in Orlando, Florida.
6. My path into the field of gender medicine is unique. For my first 20 plus years in practice, young people with transgender identity were an extremely rare phenomenon. While gay,

lesbian, and gender non-conforming patients were not uncommon, none of the patients in my care were declaring a transgender identity.

7. However, in 2015, I began to see young patients, exclusively adolescent females, who asserted that they were transgender. I was surprised that the cases I was seeing had "come out" around and after puberty. This sudden epidemiological change did not agree with what I had learned.

8. Historically, gender identity disorder and gender dysphoria affected primarily pre-pubescent boys. These young boys were adamant about their female identity. Gender dysphoria was obvious to the family, and had begun at a young age (approximately 3-5 year old), long before children are developmentally capable of hiding facts from their parents. This presentation of cross-sex identification has been described in the literature as "persistent, insistent and consistent." The rare cases of such young boys (and on an even rarer occasion, girls) did not have to "come out."

9. I now know that my experience with seeing this unusual cohort of adolescents with no history of "persistent, insistent and consistent" cross-sex identity in early childhood closely mirrors the trends seen by other clinicians. In the last eight years there has been an unexplained, dramatic rise in adolescents declaring distress with their sexed bodies and seeking hormones and surgeries to stop the development of secondary sex characteristics.

10. These puzzling epidemiological shifts made me eager to learn what is known about pediatric gender transition. This has involved reading hundreds of papers in this field that have encompassed research, practice guidelines, epidemiology, opinions, history, and ethics. This reading has been from journals that include the NEJM, JAMA, Pediatrics, British Medical Journal, Lancet, Archives of Sexual Behavior, Journal of Homosexuality, Sexual Medicine,

the Journal of American Academy of Child and Adolescent Psychiatry, American Psychologist, PLOS ONE, the Journal of Clinical Endocrinology and Metabolism, and many others. I have also studied professional guidelines from Finland, Sweden, Australia, New Zealand, England, France, and The Netherlands.

11. Importantly, I have also read the first-person accounts of patients in the lay literature, where patient stories and professional concerns are increasingly being voiced. It is my opinion that concerns regarding the so-called "gender-affirmative care model" are often barred from the medical literature.

12. My comprehensive review of the literature revealed that public health authorities in a number of progressive European countries have conducted independent evaluations of the evidence. They have found the evidence for youth transition to be lacking, any benefits to be of very low certainty, and the harms significant.

13. The risks of "gender-affirmative care" in youth are real and the harms are considerable. The most self-evident risk is that the treatment frequently leads to infertility. In fact, if the Endocrine Society's treatment recommendations for youth are followed, and puberty blockers are followed by cross-sex hormones, sterility is nearly assured. Other risks are less certain, but alarming evidence is emerging that bone health is adversely affected. A growing list of concerns includes the effect on developing brains, cardiovascular complications of cross-sex hormones, increased risk for cancer, and others. Arguably the greatest harms are regret and detransition after irreversible bodily changes, sterilization, and impairment of sexual function that is wrought by hormones and surgery.

14. The unfavorable risk/benefit ratio of pediatric transition is the reason why a growing number of liberal western countries are now sharply scaling back the practice of pediatric gender transition.

15. I have always had a keen interest in medical ethics and often considered formal education in the field. I originally wanted to explore the merging of medicine and business—hospital systems dominating the marketplace and physicians becoming employees—and how this evolution was impacting the ethics of medical care. What I was learning about gender dysphoria further propelled my interest in an ethics degree. I undertook a study of bioethics, completing my master's degree in bioethics in 2020.

16. In my degree, much effort was focused on the growing popularity of the so-called "gender-affirmative care," which delivers life-altering, permanent interventions to minors that involve sterilizing procedures. I have focused on ethical dilemmas, such as whether minors have the capacity to give a meaningful informed consent.

17. My research has given me the opportunity to work with experts in the field of gender medicine from all over the world, including Sweden, Finland, England, Australia, Canada, and the United States. I have lectured with Dr. Rittakerttu Kaltiala, a child and adolescent psychiatrist and a leading world expert in transgender care for youth. Dr. Kaltiala was instrumental in recently changing Finland's national transgender practice guidelines, when they recognized the harms being done to youth. I have also lectured on this topic to The National Academy of Science in France. I am a member of the group's scientific council. Recently, my letter outlining concerns with the practice of pediatric gender transition was

published by JAMA Pediatrics. [1] I have authored several recent manuscripts that are currently under review.

18. To round out my academic grasp of the ethical issues, I have also engaged with individuals who transitioned as youth. Some have detransitioned. Some have remained transitioned. I have learned a lot from these brave patients who have been the trailblazers in the highly experimental field of pediatric gender transition.

19. I approach gender dysphoria, gender medicine, and transgender patients from both the clinical and the ethical perspectives. First and foremost, clinical care for patients that suffer from gender dysphoria must offer the greatest benefits. Care must aim for optimal psychological, physical, sexual, and reproductive well-being. Benefits must exceed harms. The well-respected medical truism must prevail: First, do no harm.

20. I will devote part of this declaration to the profound ethical concerns that all physicians should have when treating children with gender dysphoria with medical interventions. It is my conclusion as a bioethicist that the practice of prescribing puberty blockers, cross-sex-hormones, and surgeries to minors violates every key principle of biomedical ethics.

21. Based on numerous conversations and interactions with other pediatricians, it is my opinion that many share my concerns about the unusually high numbers of adolescents requesting gender reassignment and the "gender-affirming care" they are given. Many providers are concerned about the irreversible, profound, life-long changes that these poorly evidenced interventions entail. However, in our current climate, where political activism has taken over

[1] Hunter PK. Political Issues Surrounding Gender-Affirming Care for Transgender Youth. *JAMA Pediatr*. Published online December 20, 2021. doi:10.1001/jamapediatrics.2021.5348

the medical profession, my colleagues are too afraid to speak out publicly. They fear being accused of "transphobia," or fear losing their employment.

22. Gender-dysphoric youth are suffering, and they deserve our compassion and care. The question is not *whether to treat them*, but rather, *how to treat them* in a way that promotes their long-term health and well-being. It is my strong opinion, supported by a growing number of leading pediatric gender clinics and public health authorities in the western world, that hormonal and surgical interventions should be reserved for mature adults, while minors should be treated with supportive psychological care.

23. This is because many minors will find that their trans identity is a transient phase in their identity formation—a realization that is increasingly common among previously trans-identified youth. There is a growing visibility of detransitioned young adults. They regret that they were allowed to get the interventions they so disparately desired at the time, but now realize these interventions were a mistake. Those who persist in their transgender identity can undergo interventions as adults and can be highly successful in their transition. We have many visible examples of successful transitioned adults.

24. One symbol of the medical profession is Asclepias's Rod, with a single snake wrapped around the rod. The rod is the walking stick that the physician uses to travel from home to home to care for those in need. The snake as a reminder, to both physician and patient, that the physician has the power to both heal and to harm.[2]

25. Below, I outline my position that "gender-affirmative" hormonal and surgical interventions for minors on the balance do more harm than good, and that these interventions should be

[2] Cavanaugh TA. *Hippocrates' Oath and Asclepius' Snake*. Vol 1. Oxford University Press; 2017. doi:10.1093/med/9780190673673.001.0001

delayed until a young person's identity is stabilized, full maturity is reached, and true informed consent is attainable.

II. Summary of Key Positions

Below is a summary of my key opinions. I will expand on these opinions further.

- Gender identity is not biologically predetermined
- Transgender identity in young people typically resolves
- The original research on which the practice of pediatric transition rests no longer applies to the currently presenting cases
- There is no established standard of care for transgender-identified youth
- "Gender-affirming" interventions for youth cannot be ethically justified

III. Key Positions

A. Gender Identity is not biologically predetermined

26. Proponents of treating young people with "gender-affirming" hormones and surgeries assert that gender identity is biologically predetermined and, therefore, immutable. They argue that gender-dysphoric adolescents were born "transgender" and will always be "transgender"—much like children born with a congenital disorder such as a cleft palate. Thus, they argue that it is cruel and nonsensical to delay physical alterations to the bodies needed to make their future lives easier.

27. If one is to believe gender identity is biologically predetermined and immutable, and children presenting with gender dysphoria are simply "transgender children" who were born with a

brain-body mismatch, a person holding such beliefs would reason that medical doctors should try to intervene as early as possible to "fix" the body. This is exactly the rationale that the expert witnesses for the plaintiffs in this case are presenting.

28. However, these claims are patently untrue. Despite decades of trying to prove that gender identity is biologically predetermined, the body of evidence points to something entirely different: that biology is far from deterministic, and that a transgender identity arises instead in response to is a combination of factors.

29. Below I present some of the arguments that demonstrate decisively that "gender identity" is not biologically predetermined.

i. Brain studies have not been able to demonstrate a "transgender brain"

30. Despite a number of brain studies that attempted to demonstrate that there is a distinctive brain structure that differentiates people with a transgender identity from the rest, no study has been able to demonstrate a pattern or structure unique to the "transgender brain." The few differences that have been noted disappear after researchers control for sexual orientation and exposure to hormonal interventions that gender dysphoric people undergo, or the studies are too small or unable to control for these or other known confounding factors. Brain

researchers clearly state that their findings do not justify statements suggesting gender dysphoria is a biological condition. [3, 4, 5, 6]

ii. Identical twin studies challenge the notion that gender identity is biologically predetermined

31. Identical twin studies represent one the best available methods to test biological determinism. If gender identity were to be predetermined by one's biology whereby certain children are simply born with a "transgender brain," we would expect both identical twins to have a concordant gender identity majority of the time. Instead, the research into pairs of identical twins shows that if one of the identical twins has a transgender identity the chance that the other twin is also transgender identified is less than 30%.[7]

32. It should be noted that a 30% transgender identity concordance found in identical twins is much higher than would occur by chance, which raises the possibility of biological influence for the formation of a transgender identity, alongside other possibilities. However, the 70% discordance in identical twins' transgender identity strongly signals that a transgender identity is not predetermined by one's genes or prenatal factors.

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[3] Mueller SC, De Cuypere G, T'Sjoen G. Transgender Research in the 21st Century: A Selective Critical Review From a Neurocognitive Perspective. *AJP*. 2017;174(12):1155-1162. doi:10.1176/appi.ajp.2017.17060626

[4] Frigerio A, Ballerini L, Valdés Hernández M. Structural, Functional, and Metabolic Brain Differences as a Function of Gender Identity or Sexual Orientation: A Systematic Review of the Human Neuroimaging Literature. *Arch Sex Behav*. 2021;50(8):3329-3352. doi:10.1007/s10508-021-02005-9

[5] Mueller SC, Guillamon A, Zubiaurre-Elorza L, et al. The Neuroanatomy of Transgender Identity: Mega-Analytic Findings From the ENIGMA Transgender Persons Working Group. *The Journal of Sexual Medicine*. 2021;18(6):1122-1129. doi:10.1016/j.jsxm.2021.03.079

[6] Mueller SC, Guillamon A, Zubiaurre-Elorza L, et al. The Neuroanatomy of Transgender Identity: Mega-Analytic Findings From the ENIGMA Transgender Persons Working Group. *The Journal of Sexual Medicine*. 2021;18(6):1122-1129. doi:10.1016/j.jsxm.2021.03.079

[7] Diamond M. Transsexuality Among Twins: Identity Concordance, Transition, Rearing, and Orientation. *International Journal of Transgenderism*. 2013;14(1):24-38. doi:10.1080/15532739.2013.750222

iii. Peer-reviewed publications acknowledge that transgender identity arises in response to a complex interplay of multiple factors

33. The fact that transgender identity emerges due to the interplay of a multitude of factors, rather than having a biological cause, is widely recognized. In fact, Dr. Rosenthal, one of the expert witnesses for the plaintiffs acknowledged this in his 2014 study:[8]

> *... studies have demonstrated that "gender identity"—a person's inner sense of self as male, female, or occasionally a category other than male or female—...likely reflects a complex interplay of biological, environmental, and cultural factors."* (*Rosenthal, 2014, p. 4379*)

iv. The "gender identity" theory has never been properly tested

34. While it is evident that some people have a transgender identity, and "gender dysphoria" is a diagnosable DSM-5 psychological disorder, what "gender identity" is more generally, and whether and how it varies from one's awareness of one's sex for the rest of the population, is yet to be elucidated. The claims that "everyone has a gender identity," and that one's gender identity is a different entity than one's awareness of one's own sex, have never been put to test.

35. It is worth noting that the very concept of a "gender identity" is relatively new, popularized by the psychologist Dr. John Money in the 1960's. Dr. Money's theories about gender identity developed as he experimented on identical twin boys, one of whom was being raised

[8] Rosenthal SM. Approach to the Patient: Transgender Youth: Endocrine Considerations. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99(12):4379-4389. doi:10.1210/jc.2014-1919

as a girl at Dr. Money's advice. Dr. Money made this recommendation following a circumcision accident that left the boy without a penis. To help the twin raised as a girl embrace his female gender role, Dr. Money performed highly unethical experiments on the boys, including making the siblings examine each other's genitals and perform simulated sexual acts with one another.

36. Initially, the twin boy raised as a girl appeared to have embraced the female identity, which Dr. Money took as validation of his gender identity theory. However, the twin raised in the female gender role eventually re-identified with his biological sex. Tragically, both twins died young, one from a suicide, and the other from a drug overdose. [9] The parents of the twins blamed Dr. Money's experiments as contributing to their sons' mental health struggles and premature death.

37. The proponents of "gender-affirming" hormonal and surgical interventions for minors claim that Dr. Money's experiments proved that gender identity is biologically predetermined and immutable (since the child raised as a girl eventually identified as a boy, despite the psychologist's efforts to the contrary). However, few conclusions can be drawn from a single case that involved such unusual circumstances.

38. More than anything, this experiment demonstrates the problematic origins of the gender identity theory and highlights the profound ethical problems with the currently ongoing social, medical, and surgical experimentation on minors in an attempt to deny or obfuscate their sex.

[9] John Colapinto., 2013. *As nature made him: the boy who was raised as a girl*. HarperCollins Publishers.

B. Transgender identity in young people typically resolves

39. During childhood, adolescence, and young adulthood, an individual's identity continues to develop and change. Historical data shows that most cases of a cross-sex identity in children resolve before they reach mature adulthood. Research confirms that the majority of such youth grow up to be gay, lesbian, or bisexual adults. In fact, a period of cross-sex identification in childhood is a common developmental pathway of gay adults.[10, 11]

40. Contrary to the assertions of the proponents of "gender affirmation," the tendency of a cross-sex identity to resolve is not coerced, but rather happens through the natural course of undergoing puberty and reaching maturity. While the mechanism by which this change occurs is not exactly known, it has been observed that experiencing romantic and sexual encounters and undergoing physical changes of puberty play a key role. [12,13]

41. In talking about the permanent vs. transient nature of transgender identity, is important to differentiate between two known variants of gender dysphoria in young people: the "classical" presentation where gender dysphoria begins in early childhood (typically between ages 3-5), and the novel and now-predominant variant where older children "come out" as transgender around or after the onset of puberty.

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[10] *See* Cantor, 2020

[11] Korte A, Goecker D, Krude H, Lehmkuhl U, Grüters-Kieslich A, Beier KM. Gender Identity Disorders in Childhood and Adolescence. *Dtsch Arztebl Int*. 2008;105(48):834-841. doi:10.3238/arztebl.2008.0834

[12] Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clin Child Psychol Psychiatry*. 2011;16(4):499-516. doi:10.1177/1359104510378303

[13] Kaltiala-Heino R, Bergman H, Työläjärvi M, Frisen L. Gender dysphoria in adolescence: current perspectives. *AHMT*. 2018;Volume 9:31-41. doi:10.2147/AHMT.S135432

i. Childhood-onset gender dysphoria typically remits naturally

42. To date, the total of 11 studies have been conducted to determine the trajectories of children with early-childhood onset of gender dysphoria. All 11 demonstrated that for a majority of such children (61%-98%), early childhood-onset gender dysphoria resolves without any interventions by late adolescence or young adulthood. [14, 15,16]

43. Proponents of pediatric "gender-affirmation" reject this proven high rate of desistance. The fact that desistence happens so frequently in gender-dysphoric children is a threat to the premise of pediatric gender transition. In fact, the expert witnesses for the plaintiffs go to great lengths to preemptively discredit the statistic.

44. For example, Dr. Hawkins attempts to discredit the overwhelming evidence that pediatric gender dysphoria typically self-resolves by claiming that the prior studies dealt with merely gender-non-conforming "non-transgender children," rather than "true transgender children." Hawkins says, "*Historically, earlier studies included a wide range of gender nonconforming children, rather than differentiating between transgender and non-transgender children, and also suffered from other serious methodological flaws that make them unreliable."* (Hawkins, para 22)

45. This claim is not credible at face value. The studies in question have been authored by the very same researchers who are their countries' respective leaders in pediatric gender

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[14] Cantor JM. Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy. *Journal of Sex & Marital Therapy*. 2020;46(4):307-313. doi:10.1080/0092623X.2019.1698481

[15] Ristori J, Steensma TD. Gender dysphoria in childhood. *International Review of Psychiatry*. 2016;28(1):13-20. doi:10.3109/09540261.2015.1115754

[16] Singh D, Bradley SJ, Zucker KJ. A Follow-Up Study of Boys With Gender Identity Disorder. *Front Psychiatry*. 2021;12. doi:10.3389/fpsyt.2021.632784

transition. These are the very same authors who have produced much of the currently available literature upon which the entire field of pediatric gender transition rests. To suggest that these clinicians and researchers were somehow confused about their own study subjects, and accidentally studied children who were merely "tomboy girls" or "feminine boys," rather than children with significant gender identity issues, is to imply that the entire body of evidence in the field of pediatric gender medicine came from highly confused clinicians and researchers.

46. Hawken's argument is not original—the proponents of pediatric gender transition have been making it for some time. In response to their critique, a prominent researcher in the field of pediatric gender medicine, Dr. Ken Zucker, re-analyzed the studies in question and split the study subjects into two cohorts: those who were extremely gender non-conforming but did not meet the full diagnostic criteria for Gender Identity Disorder (which was the name of the respective DSM diagnosis at the time), and those who actually met the full diagnostic criteria for having Gender Identity Disorder.

47. The reanalysis confirmed the original finding that most children diagnosed with a gender issue per DSM—nearly 7 in 10—naturally stopped identifying as transgender by the time they reached adulthood. The rate of natural resolution for gender dysphoria is even higher, more than 9 in 10, for those who gender distress was significant enough to warrant a consult with a pediatric gender clinic, but not enough to meet the full diagnostic DSM criteria. [17]

[17] Zucker KJ. The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). *International Journal of Transgenderism*. 2018;19(2):231-245. doi:10.1080/15532739.2018.1468293

48. Yet another way that pro-transition activists have tried to discredit the well-established fact that childhood gender dysphoria eventually remits, is by claiming that DSM-IV criteria used at the time were so flawed as to be totally invalid. These claims assert that even those properly diagnosed with "Gender Identity Disorder" in DSM-IV were not "transgender" at all, but were merely gender-non-conforming.

49. While it is true that the updated DSM-5 criteria in use today made some changes to the childhood diagnosis, these changes have proven to be minor and not clinically significant. Both of the diagnostic manuals (the prior DSM-IV and the current DSM-5) were recently field-tested and were found to be equivalent in terms of which children they flagged as meeting the diagnostic criteria: [18]

> "…*both editions (DSM-IV and DSM-5 and ICD-10 and ICD-11) of gender identity-related diagnoses seem reliable and convenient for clinical use."*

50. The Chair of the DSM-5 Work Group for Sexual and Gender Identity Disorders also concurs that the change in the diagnostic criteria for children from DSM-IV to DSM-5 was not significant: [19]

> *"It is my clinical opinion that the similarities across the various iterations of the DSM are far greater than the differences (Zucker, 2010) and, as part of the work done by the Subcommittee on Gender Identity Disorders for the DSM-IV, provided one example of this (Zucker et al., 1998)*

[18] de Vries ALC, Beek TF, Dhondt K, et al. Reliability and Clinical Utility of Gender Identity-Related Diagnoses: Comparisons Between the ICD-11, ICD-10, DSM-IV, and DSM-5. *LGBT Health*. 2021;8(2):133-142. P.1 doi:10.1089/lgbt.2020.0272

[19] Zucker KJ. The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). *International Journal of Transgenderism*. 2018;19(2):231-245. doi:10.1080/15532739.2018.1468293

51. Thus, the argument that the high desistance rates of pediatric gender dysphoria recorded in all the studies to date were due to the mistaken inclusion of merely gender-non-conforming, rather than "truly transgender" children, does not hold up. It is undeniable that most gender dysphoric children will not grow up to be transgender identified adults, as long as they are allowed to naturally develop without undergoing social and medical transition.

52. Further, contrary to the unfounded plaintiff expert witnesses' claims, no clinician can accurately predict which of the trans-identified children will continue to identify as transgender in mature adulthood vs. those that will desist. This is recognized by the seminal study evaluating the development trajectories of gender-distressed children.[20]

> *"When considering the development of children with GD [gender dysphoria]; studies show that gender dysphoric feelings eventually desist for the majority of children with GD, and that their psychosexual outcome is strongly associated with a lesbian, gay, or bisexual sexuality which does not require any medical intervention, instead of an outcome where medical intervention is required (e.g. Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Singh, 2012). Factors predictive for the persistence of GD have been identified on a group level, with higher intensity of GD in childhood identified as the strongest predictor for a future gender dysphoric outcome (Steensma et al., 2013).* ***The predictive value of the identified factors for persistence are, however, on an individual level less clear cut, and the clinical utility of currently identified factors is low****" (Ristori and Steensma, 2016, p. 6)*

[20] Ristori J, Steensma TD. Gender dysphoria in childhood. *International Review of Psychiatry*. 2016;28(1):13-20. doi:10.3109/09540261.2015.1115754

53. This very inability to predict who will persist vs. desist raises serious ethical questions regarding the provision of any irreversible procedures, and particularly those that result in sterilization.

54. The common claim by medicalization activists that once a gender-dysphoric minor reaches adolescence, their gender identity is fixed, is not supported by the evidence. In the 11 desistance studies, the age at which the subjects were followed ranged from adolescence into young adulthood. Some desisted in puberty and others in young adulthood. The Endocrine Society's treatment guidelines acknowledge this:[21]

> *"With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence* ***and adulthood*** *(so-called "desisters"). (Hembree et al., 2017, p. 3876)*

ii. Transgender identity in adolescents has an unknown developmental trajectory, but high rates of mutability are increasingly evident

55. It is now well recognized that a new variant of transgender identity emerged in the mid 2015's, represented by young people who were not cross-sex identified in childhood. Such cases were virtually unseen until about 7-10 years ago. This is the very population I, and many of my colleagues in the US and internationally, are now seeing in our practices. If one can develop a transgender identity for the first time in adolescence, it demonstrates that a transgender identity is not fixed.

[21] Hembree WC, Cohen-Kettenis PT, Gooren L, et al. ENDOCRINE TREATMENT OF GENDER-DYSPHORIC/GENDER-INCONGRUENT PERSONS: AN ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINE. *Endocrine Practice*. 2017;23(12):1437-1437. doi:10.4158/1934-2403-23.12.1437

56. The UK has one of the biggest pediatric gender clinics in the world. The UK clinicians made this observation recently regarding adolescents declaring a trans identity without any childhood history: [22]

> *'...some of us have informally tended toward describing the phenomenon we witness as "adolescent-onset" gender dysphoria, that is,* ***without any notable symptom history prior to or during the early stages of puberty*** *(certainly nothing of clinical significance.)"*(Hutchinson et al., 2020, p. 1)

57. The lead researcher for the Finnish national pediatric gender services program, one of the most respected in the world, has stated the following: [23]

> *"In Finland most adolescents seeking medical treatment in order for their body to conform with their gender identity do not fulfil the eligibility criteria ... for example because they initially* ***experienced onset of gender dysphoria in the late stages of pubertal development*** *or suffer from severe mental disorders which predate the onset of gender dysphoria. Research on adolescent onset gender dysphoria is scarce, and optimal treatment options have not been established [12]. The reasons for the sudden increase in treatment-seeking due to* ***adolescent onset gender dysphoria*** */ transgender identification are not known [13]"* (Kaltiala-Heino and Lindberg, 2019, p. 62)

[22] Hutchinson A, Midgen M, Spiliadis A. In Support of Research Into Rapid-Onset Gender Dysphoria. *Arch Sex Behav*. 2020;49(1):79-80. p.1 doi:10.1007/s10508-019-01517-9

[23] Kaltiala-Heino R, Lindberg N. Gender identities in adolescent population: Methodological issues and prevalence across age groups. *Eur psychiatr*. 2019;55:61-66. p.62 doi:10.1016/j.eurpsy.2018.09.003

58. A leading Canadian pediatric gender expert made a similar observation: [24]

> *".. it is my view (and that of others) that a new subgroup of adolescents with gender dysphoria has appeared on the clinical scene. This subgroup appears to be comprised—at least so far—of a disproportionate percentage of birth-assigned females* ***who do not have a history of gender dysphoria in childhood or even evidence of marked gender-variant or gender nonconforming behavior****."* (Zucker, 2019, p. 4)

59. Last but not least, even the principal investigator of the medical protocol for transitioning minors (known as the Dutch Protocol) recently acknowledged that a fundamental shift has occurred where adolescents are "coming out" with a trans identity around puberty:[25]

> *"... gender identity development is diverse, and a new developmental pathway is proposed involving youth with postpuberty* ***adolescent-onset transgender histories****.6–8 These youth did not yet participate in the early evaluation studies.5,9" (de Vries, 2020, p. 1)*

[24] Zucker KJ. Adolescents with Gender Dysphoria: Reflections on Some Contemporary Clinical and Research Issues. *Arch Sex Behav*. 2019;48(7):1983-1992. doi:10.1007/s10508-019-01518-8

[25] de Vries ALC. Challenges in Timing Puberty Suppression for Gender-Nonconforming Adolescents. *Pediatrics*. 2020;146(4):e2020010611. doi:10.1542/peds.2020-010611

60. Finally, the growing visibility of young adult detransitioners confirms that a transgender identity can desist in young people. [26, 27, 28, 29]

61. A recent study from a UK adult gender clinic showed that over 10% of young people treated with gender-affirmative interventions detransitioned within 16 months of starting treatment. Another 22% of patients disengaged from the clinic without completing their treatment plan.[30]

62. Another clinic population study found that over 12% of those who had started hormonal treatments either detransitioned or documented regret, while 20% stopped the treatments for a wider range of reasons. These patients presented to the clinics as young adults (mean age of 20) and it took them on average 5 years from beginning treatment to stopping it. Notably, the UK researchers said this: [31]

> *"Thus, the detransition rate found in this population is novel and questions may be raised about the phenomenon of overdiagnosis, overtreatment, or iatrogenic harm as found in other medical fields." (Boyd et al., 2021, p.12)*

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[26] Entwistle K. Debate: Reality check – Detransitioner's testimonies require us to rethink gender dysphoria. *Child Adolesc Ment Health*. Published online May 14, 2020:camh.12380. doi:10.1111/camh.12380

[27] Littman L. Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners. *Arch Sex Behav*. Published online October 19, 2021. doi:10.1007/s10508-021-02163-w

[28] Levine SB, Abbruzzese E, Mason JM. Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults. *Journal of Sex & Marital Therapy*. Published online March 17, 2022:1-22. doi:10.1080/0092623X.2022.2046221

[29] Vandenbussche E. Detransition-Related Needs and Support: A Cross-Sectional Online Survey. *Journal of Homosexuality*. Published online April 30, 2021:20. doi:10.1080/00918369.2021.1919479

[30] Hall R, Mitchell L, Sachdeva J. Access to care and frequency of detransition among a cohort discharged by a UK national adult gender identity clinic: retrospective case-note review. *BJPsych open*. 2021;7(6):e184. doi:10.1192/bjo.2021.1022

[31] Boyd IL, Hackett T, Bewley S. Care of Transgender Patients: A General Practice Quality Improvement Approach. *SSRN Journal*. Published online 2021. p. 12 doi:10.3390/healthcare10010121

63. Further, we have direct evidence that adolescents with a transgender identity who desire to undergo medical interventions but are told to wait will likely desist. While the studies into this subject are scarce, in the early 2000's Dutch researchers (who pioneered the practice of pediatric gender transition) followed 14 adolescents who were rejected from hormonal and surgical interventions due to presenting with co-morbid mental health issues. [32]

64. At follow-up when the subjects were in their 20's, approximately 1-7 years after being rejected from medical transition as minors, the researchers discovered that 11 of 14 cases no longer wished to transition at all, two subjects only slightly regretted not being able to transition, and only one subject continued to strongly wish to transition. This single subject only wanted breast augmentation, but no other surgery in order to preserve sexual function.[33] Had that one individual been transitioned as a minor under the Dutch protocol, the loss of fertility and sexual function would have ensued.

65. Thus, all 14 of the 14 who were rejected from gender reassignment as teens benefitted from the intervention being delayed until they reached mature adulthood. These 14 young adults simultaneously prove three things: (i) Desistance frequently occurs. (ii) Desistence occurs even when gender dysphoria persists into adolescence. And (iii) a transgender identity is not immutable.

[32] Smith YLS, Van Goozen SHM, Cohen-Kettenis PT. Adolescents With Gender Identity Disorder Who Were Accepted or Rejected for Sex Reassignment Surgery: A Prospective Follow-up Study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001;40(4):472-481. doi:10.1097/00004583-200104000-00017

[33] Malone W, D'Angelo R, Beck S, Mason J, Evans M. Puberty blockers for gender dysphoria: the science is far from settled. *The Lancet Child & Adolescent Health*. 2021;5(9):e33-e34. doi:10.1016/S2352-4642(21)00235-2

iii. The terms "transgender child" or "transgender adolescent" are poorly defined

66. Precisely because no clinician can reliably predict which young person will desist from their transgender identification vs. who will persist, the notion of a "transgender child/adolescent" extensively used by the plaintiff's witnesses is not a valid one.

67. "Transgender" is not a diagnosis found in any of the existing diagnostic classifications (either DSM or ICD). It's a lay term that has a wide range of definitions that vary depending on each person's unique understanding of this phenomenon.

68. I maintain that the use of the adjective "transgender" by the plaintiffs' expert witnesses, whenever they talk about gender-dysphoric youth, aims to create an emotional response, implies immutability not supported by evidence, and generally does not belong in a legal document dealing with medical interventions as it lacks a clinical definition. The proper terms in medical contexts are "gender-dysphoric" or "diagnosed with gender dysphoria," based on the diagnostic DSM-5 criteria that are currently in use in the United States.

C. The original research on which the practice of pediatric transition rests no longer applies to the currently presenting cases

i. The Protocol for gender-transitioning minors suffers from serious problems.

69. The practice of pediatric gender transition, known as "gender-affirmative care," rests on a single experiment from the Netherlands conducted circa 2010. This small, single-site, uncontrolled experiment showed that carefully selecting only the highest-functioning children with no mental health problems aside, from being cross-sex identified from early childhood on, and providing them with puberty blockers and cross-sex hormones upon reaching mid-adolescence, followed by surgeries after reaching the 18th birthday, allows

these children to continue to be high-functioning approximately 1.5 years after the completion of final surgery. [34,35]

70. However, the only attempt to replicate the Dutch experiment outside the Netherlands, in the world's largest gender clinic in the UK, failed to show any positive outcomes of the first phase of the Dutch protocol (puberty blockers).[36] The latter phases of the Dutch protocol (following puberty blockers with cross-sex hormones and surgery) have never been attempted to be replicated.

71. Further, new information came into light recently that suggests that the Dutch experiment was both misunderstood and misrepresented as providing "proof" that gender reassignment for minors leads to successful outcomes, when in fact, the study's conclusions are highly questionable. For example, while the Dutch researchers took credit for the adolescents' high level of functioning after transition, these adolescents were high functioning before transition due to the study's stringent participant selection criteria.

72. In fact, for half of the psychological measures tracked, there were no statistically significant improvements before vs. after the treatment protocol. The positive changes in the rest of the psychological measures were so small as to be of highly questionable clinical significance,

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[34] de Vries ALC, Steensma TD, Doreleijers TAH, Cohen-Kettenis PT. Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study. *The Journal of Sexual Medicine*. 2011;8(8):2276-2283. doi:10.1111/j.1743-6109.2010.01943.x

[35] de Vries ALC, McGuire JK, Steensma TD, Wagenaar ECF, Doreleijers TAH, Cohen-Kettenis PT. Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment. *Pediatrics*. 2014;134(4):696-704. doi:10.1542/peds.2013-2958

[36] Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. Santana GL, ed. *PLoS ONE*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894

and could not be attributed to the hormones and surgeries alone since all the subjects also received extensive psychological support. [37]

73. More generally, the lack of a control group rendered the study findings "very low certainty," the rating assigned to the study by the recent comprehensive systematic review of evidence conducted by the UK's National Institute for Health and Care Excellence (NICE). [38]

74. Even the study's most-lauded finding, the marked drop in the "gender dysphoria" score, is now in question, as it has come to light that the researchers did not have an appropriate scale to capture changes in gender dysphoria, and they used the scale that they did have access to in a highly questionable way (by "flipping" the male and female versions of the scales between baseline and final measurement time periods).[39]

75. Further, the Dutch team had very strict screening criteria, which would have excluded the vast majority of young people who request gender reassignment today. For example, the Dutch excluded from their experiment any adolescent whose transgender identity emerged only around and after puberty—they required that clear cross-sex identification be present from very early childhood on. The Dutch also excluded the adolescents who were suicidal or had any significant unaddressed mental illness. Adolescents with a non-binary identity were not eligible. In addition, the Dutch researchers insisted that the adolescents have a firm grasp

[37] *See* Levine, 2020

[38] National Institute for Health and Care Excellence. Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria. https://web.archive.org/web/20220414202655/https://arms.nice.org.uk/resources/hub/1070905/attachment

[39] *See* Levine, 2020

of biological reality and realize they will never be able to become the "opposite sex" despite the hormonal and surgical interventions. [40, 41]

76. Several children in the small sample of 70 cases (which, by the end of the study, shrank to 55) experienced severe adverse events while under treatment, including one young adult who died followed surgical complications, several cases of new diabetes and obesity, and at least one case of detransition, although the study is vague on this point.[42]

77. This study, and the modest psychological improvements reported, came at the cost of sterility for 100% of the subjects (mandatory removal of ovaries and testes was part of the protocol), and were associated with severe adverse, raising serious ethical concerns that I will address later on in more detail.

78. The concern that I would like to focus on here is that the presentation of gender dysphoria in youth has markedly changed since the Dutch protocol's final results were published in 2014. As a result, the continued application of this protocol to the populations for which it was never intended in the first place is not justified under any circumstances. This misapplication of the Dutch protocol directly contradicts the principle of evidence-based medicine.

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[40] Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *eur j endocrinol*. 2006;155(suppl_1):S131-S137. doi:10.1530/eje.1.02231

[41] Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJG. The treatment of adolescent transsexuals: changing insights. *J Sex Med*. 2008;5(8):1892-1897. doi:10.1111/j.1743-6109.2008.00870.x

[42] *See* de Vries et al., 2014

ii. The vast majority of currently presenting cases of gender dysphoric youth no longer meet the strict criteria of the Dutch protocol

79. Currently, approximately 2%-9% of minors in the US identify as transgender.[43,44] Most are adolescent females who "came out" as transgender around the time of puberty, and very often have significant mental health comorbidities that pre-date the onset of transgender identity. [45, 46, 47] Increasingly, these minors are identifying as "non-binary": neither male nor female, or both as male and female.[48] Recent research estimates that as many as 67% of trans-identified adolescents today identify as non-binary. [49]

80. The new clinical presentation and skyrocketing numbers are totally new phenomena. As recently as eight or ten years ago, seeing a child with a cross-gender identity was extremely rare, and most were prepubescent boys, the majority of whom outgrew their trans

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[43] Johns MM, Lowry R, Andrzejewski J, et al. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students - 19 States and Large Urban School Districts, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(3):67-71. doi:10.15585/mmwr.mm6803a3

[44] Kidd KM, Sequeira GM, Douglas C, et al. Prevalence of Gender-Diverse Youth in an Urban School District. *Pediatrics*. 2021;147(6):e2020049823. doi:10.1542/peds.2020-049823

[45] Becerra-Culqui TA, Liu Y, Nash R, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics*. 2018;141(5):e20173845. doi:10.1542/peds.2017-3845

[46] Kaltiala-Heino R, Sumia M, Työläjärvi M, Lindberg N. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child Adolesc Psychiatry Ment Health*. 2015;9(1):9. doi:10.1186/s13034-015-0042-y

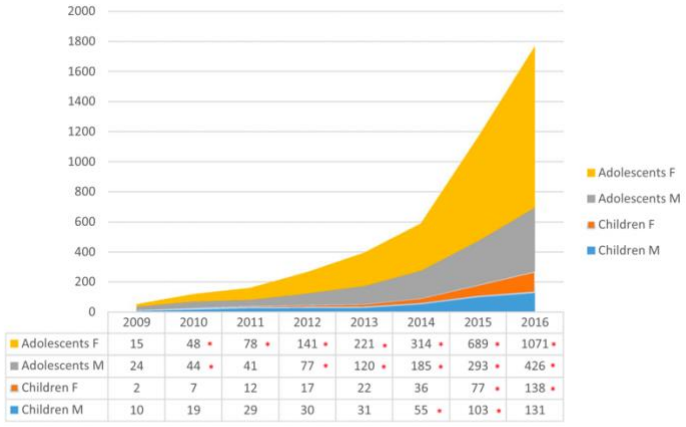
[47] Kaltiala-Heino R, Lindberg N. Gender identities in adolescent population: Methodological issues and prevalence across age groups. *Eur psychiatr*. 2019;55:61-66. doi:10.1016/j.eurpsy.2018.09.003

[48] Chew D, Tollit MA, Poulakis Z, Zwickl S, Cheung AS, Pang KC. Youths with a non-binary gender identity: a review of their sociodemographic and clinical profile. *The Lancet Child & Adolescent Health*. 2020;4(4):322-330. doi:10.1016/S2352-4642(19)30403-1

[49] Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *Journal of Adolescent Health*. Published online December 2021:S1054139X21005681. doi:10.1016/j.jadohealth.2021.10.036

identification sometime before mature adulthood. Many of these youths grew up to be gay. [50] [51]

81. The graph shown here from the Gender Identity Service in England is but one example of this worldwide phenomenon.[52]



	2009	2010	2011	2012	2013	2014	2015	2016
Adolescents F	15	48 *	78 *	141 *	221 *	314 *	689 *	1071 *
Adolescents M	24	44 *	41	77 *	120 *	185 *	293 *	426 *
Children F	2	7	12	17	22	36	77 *	138 *
Children M	10	19	29	30	31	55 *	103 *	131

AFAB = assigned female at birth; AMAB = assigned male at birth
* Indicates $p < .05$ which shows a significant increase of referrals compared to the previous year

82. In my own practice, I am also struck by the similarities in the patient stories of trans-identified youth. Most are adolescent females who have had a normative childhood from the gender standpoint, but have felt isolated from their peers. They have had pre-existing anxiety and depression. Several have had a history of psychiatric hospitalizations.

83. What is particularly striking is that that my patients arrive at my office well-versed in gender-related terminology. The trans-identified youth I see use terms that I did not expect to hear from late elementary, middle school, and high school students. Without prompting or questioning, I often hear about self-diagnoses of depression, anxiety, PTSD, autism, and

[50] *See* Cantor, 2020, Appendix

[51] *See* Korte, 2008

[52] de Graaf NM, Giovanardi G, Zitz C, Carmichael P. Sex Ratio in Children and Adolescents Referred to the Gender Identity Development Service in the UK (2009–2016). *Arch Sex Behav*. 2018;47(5):1301-1304. doi:10.1007/s10508-018-1204-9

dissociative disorders. Terms such as *puberty blockers*, *cross sex hormones*, *fully reversible*, *partially reversible, irreversible, suicidality*, *allyship*, *misgendering*, *minority stress*, and *transphobia* are often mentioned. The patient familiarity with terminology in this field is remarkable.

84. The advocates of medicalization may celebrate this as patient empowerment and patient education. To me this suggests a heavy influence from others. These youth self-diagnose and arrive in my office certain of their condition and the need for treatment, which is usually a request for hormones.

85. The emergence of a new clinical entity, and to an unprecedented scale, would normally give us pause. A pause to better understand what's causing the exponential rise in gender dysphoria and how best to understand it and address it. Several national health systems in progressive countries have indeed done this very thing. They include Finland, Sweden, and the UK, all of which have recently conducted systematic reviews of evidence and have begun to sharply limit pediatric transition over the concerns about this new trend.

86. Instead of a pause and critical analysis of the situation, as other countries are now doing, the US presses on, oblivious to these changes, and even actively suppressing concerns. The researcher who first raised the key question of why suddenly so many teenagers, and especially females with pre-existing mental health problems, are declaring a trans identity and seeking "gender-affirming" hormones, and hypothesized that peer pressure and social influence may be playing a key role, has been subject to intimidation, abuse, and silencing.[53]

87. It should also be noted that we are currently experiencing a well-recognized and new phenomenon of high numbers of children, particularly adolescent females, developing the

[53] https://quillette.com/2018/08/31/as-a-former-dean-of-harvard-medical-school-i-question-browns-failure-to-defend-lisa-littman/

sudden onset of tics that has been tied to social contagion via social networks.[54] Other well-researched socially-mediated psychological phenomena are eating disorders. It is known that bulimia and anorexia can spread through human social networks. These human social networks existed prior to the internet, can spread these conditions, and have disproportionately affected adolescent females. [55,56]

88. I am not asserting that adolescent-onset gender dysphoria spreads through social circles or is socially contagious—however this hypothesis and others need to be investigated. It is reasonable and prudent to ask why this is happening—as many as 1 in 10 youth currently claim a transgender identity —before a growing number of children are subjected to irreversible and highly experimental medical interventions. [57]

D. There is no established standard of care for transgender-identified youth

i. Current treatment guidelines do not represent a standard of care

89. Contrary to the plaintiffs' expert reports, there is currently no established standard of care for transgender-identified youth. Instead, multiple professional societies have come up with various treatment guidelines which are increasingly divergent in terms of how to approach the management of gender dysphoria in youth.

[54] https://ipmh.duke.edu/news/pediatric-presentation-tics-potential-role-tiktok
[55] Allison S, Warin M, Bastiampillai T. Anorexia nervosa and social contagion: Clinical implications. *Aust N Z J Psychiatry*. 2014;48(2):116-120. doi:10.1177/0004867413502092

[56] Forman-Hoffman VL, Cunningham CL. Geographical clustering of eating disordered behaviors in U.S. high school students. *Int J Eat Disord*. 2008;41(3):209-214. doi:10.1002/eat.20491

[57] Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. Romer D, ed. *PLoS ONE*. 2018;13(8):e0202330. doi:10.1371/journal.pone.0202330

90. Unlike standards of care, which should be authoritative, unbiased consensus positions designed to produce optimal outcomes, practice guidelines are suggestions or recommendations. Depending on their sponsor, practice guidelines may be biased. [58]

91. The World Professional Association for Transgender Health (WPATH), an advocacy organization with a mission to remove barriers to insurance coverage for "gender-affirming" hormones and surgeries, is one of several organizations that authors guidelines in this space. Although WPATH named its guidelines "Standards of Care," it recently had to acknowledge that their recommendations are merely practice guidelines, rather than standards of care.[59]

92. The "Standards of Care 7" acknowledges that it was not evidence-based and did not utilize any systematic reviews of evidence, but rather was based on the emerging cultural changes and expert opinions of clinicians, many of whom derive a significant proportion of their income from delivering transgender medicine. A recent systematic review of treatment guidelines in this space found that "Standards of Care 7" were generally unfit for clinical decision-making, and it described several recommendations in the document as incoherent.[60]

93. The upcoming "Standards of Care 8" have not yet been finalized, but the draft version signals even more aggressive lowering of age of eligibility for hormonal and surgical interventions than that found in "Standards of Care 7," clearly signaling that the values and preferences of

[58] Malone WJ, Hruz PW, Mason JW, Beck S. Letter to the Editor from William J. Malone et al: "Proper Care of Transgender and Gender-diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective." *The Journal of Clinical Endocrinology & Metabolism*. Published online March 27, 2021:dgab205. doi:10.1210/clinem/dgab205

[59] *See* Malone et al., 2021

[60] Dahlen S, Connolly D, Arif I, Junejo MH, Bewley S, Meads C. International clinical practice guidelines for gender minority/trans people: systematic review and quality assessment. *BMJ Open*. 2021;11(4):e048943. doi:10.1136/bmjopen-2021-048943

WPATH clinicians are strongly aligned with medicalization even when the evidence for it is low-quality and non-existent entirely.

94. Another guideline that the plaintiffs' expert witnesses erroneously cite as representing the standard of care is that by the Endocrine Society. However, the Endocrine Society's guidelines clearly state: [61]

> *"…the guidelines cannot guarantee any specific outcome, nor do they establish a standard of care." (Hembree et al., 2017, p. 3895)*

95. The Endocrine Society's recommendation to halt gender dysphoric minors' puberty and treat them with cross-sex hormones is rated as "weak," and is recognized as coming from low quality evidence by the guidelines itself.[62] The "weak" grading indicates that it is not known whether the benefits outweigh the risks.

96. Notably, the only studies cited in the two key recommendations to treat minors hormonally are the two Dutch studies I described earlier.[63] Thus, the entire foundation of the Endocrine Society's recommendations to medically intervene with gender-dysphoric minors comes from a single small-scale experiment with significant problems, as described earlier.

ii. The National Institutes of Health (NIH)-funded research acknowledges that little is known about pediatric gender transition

97. According to the research protocol filed by the researchers for a recent NIH grant, the data on pediatric gender transitions are almost entirely lacking. The need to conduct this research

[61] *See* Hembree et al., 2017
[62] *See* Hembree et al., 2017
[63] *See* de Vries et al., 2011 and de Vries et al., 2014

demonstrates that this care pathway remains largely experimental, with an unknown risk-benefit ratio. [64]

98. The following quotes from the NIH grant from 2019 clearly demonstrate how immature the field of pediatric gender medicine is: [65]

- *"Although the Endocrine Society Clinical Practice Guidelines are widely adopted by providers around the United States and worldwide, there are no formal empirical studies of related clinical outcomes in transgender children and adolescents."*
- "*…existing models of care for transgender youth…have been used in clinical settings for close to a decade, although with limited empirical research to support them"*
- *"Although these [current clinical practice] guidelines have informed care at academic and community centers across the United States, they are based on very limited data. Furthermore, there is minimal available data examining the long-term physiologic and metabolic consequences of gender-affirming hormone treatment in youth. This represents a critical gap in knowledge that has significant implications for clinical practice across the United States."*
- *"The gap in existing knowledge about the impact of these practices leaves providers and caretakers uncertain about moving forward with the recommended medical interventions for transgender youth seeking phenotypic transition."*

[64] Olson-Kennedy J, Chan YM, Garofalo R, et al. Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study. *JMIR Res Protoc*. 2019;8(7):e14434. doi:10.2196/14434

[65] *See* Olson-Kennedy et al., 2019

99. These quotes, and the substantial amount of money paid by the NIH to fund this research, clearly demonstrate that "gender-affirmative" interventions are still in the experimental stage and are not yet ready to deemed either "safe" or "effective."

100. When there is no data of the benefits, and the risks are substantial, the onus is on the research community to first demonstrate that benefits that outweigh the risks. Until such evidence exists, no standard of care can be claimed.

iii. The United States is increasingly becoming an outlier in its non-evidence-based stance that transitioning minors is a safe and effective practice

101. Sweden is the first country in the world to recognize the legal status of transgender adults. In May of 2021, Sweden's flagship children's hospital, which is affiliated with the Karolinska Institute that grants the Nobel Prize of Medicine, announced that they were discontinuing all new pediatric transitions due to concerns over the lack of efficacy and the potential for significant harm. In May 2022, Sweden's Health Authority (National Board of Health and Welfare/NBHW) issued a country-wide policy that states that going forward, pediatric gender transitions will not be available in general medical practice to those <18. Such interventions will only be provided in strictly controlled clinical trial settings with a focus on the strictest ethical safeguards for youth, given the significant risk of harm.

102. It is noteworthy that the official English translation of Sweden's health authority's decision states:[66]

[66] https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf

"For adolescents with gender incongruence, the NBHW deems that the ***risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits****... This judgement is based mainly on three factors: the continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments, the new knowledge that detransition occurs among young adults, and the uncertainty that follows from the yet unexplained increase in the number of care seekers, an increase particularly large among adolescents registered as females at birth."*

103. Increasingly, a number of western countries with significant experience in pediatric gender transition are turning away from WPATH and the Endocrine Society's guidelines. In the last 24 months, not just Sweden, but also Finland, the UK, and France, after independently reviewing evidence, have issued their own guidelines that are far more conservative than the stances promoted by the US-based medical societies. [67,68,69]

104. However, in the US, the proponents of medical interventions of minors continue to assert that if a child on the verge of puberty, or an older adolescent meets the diagnostic criteria for gender dysphoria, then medical interventions are without question "medically necessary."

105. This confidence by US clinicians extends to medical interventions for "non-binary" youth who are an even less well-understood population. Procedures viewed as "medically necessary" by some of the proponents of "gender-affirmative care" for minors now include

[67] https://segm.org/Finland_deviates_from_WPATH_prioritizing_psychotherapy_no_surgery_for_minors

[68] https://cass.independent-review.uk/publications/interim-report/

[69] https://segm.org/France-cautions-regarding-puberty-blockers-and-cross-sex-hormones-for-youth

the suppression of puberty indefinitely in order to present as an ambiguous sex, [70,71] mastectomy on youth as young as 13 years of age,[72] and "non-binary" breast surgeries that preserve a feminine appearance while changing the placement of the nipples to be more reminiscent of a male chest, should the minor's identity reside somewhere along the "male to female spectrum." [73]

106. It is my belief that the highly politicized nature of the US debate about transgender healthcare has pushed our country toward an increasingly pro-medicalization position, at the same time the rest of the world is making a U-turn. The failure of the US-based medical societies to recognize the harms that are currently occurring to vulnerable minors is hard to understand, and raises serious ethical questions.

IV. Ethical Considerations and Conclusions

107. Medical ethics rests on four key pillars: the principles of patient autonomy, justice, beneficence, and nonmaleficence.[74] It is my belief as a bioethicist that providing youth with hormones and surgeries directly violates all of these principles. For this reason, it is my belief that true informed consent to "gender-affirming" hormones and surgeries for minors is not possible.

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[70] Notini L, Earp BD, Gillam L, et al. Forever young? The ethics of ongoing puberty suppression for non-binary adults. *J Med Ethics*. Published online July 24, 2020:medethics-2019-106012. doi:10.1136/medethics-2019-106012

[71] Pang KC, Notini L, McDougall R, et al. Long-term Puberty Suppression for a Nonbinary Teenager. *Pediatrics*. 2020;145(2):e20191606. doi:10.1542/peds.2019-1606

[72] Olson-Kennedy J, Warus J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. *JAMA Pediatr*. 2018;172(5):431. doi:10.1001/jamapediatrics.2017.5440

[73] https://cranects.com/non-binary-surgery/

[74]Varkey B. Principles of clinical ethics and their application to practice. *Med Princ Pract*. Published online June 4, 2020. doi:10.1159/000509119

A. The principle of "Patient Autonomy" is not respected when "gender-affirming" hormones and surgeries are provided to minors

108. Patient autonomy is a bedrock principle of medical ethics, having a long and well-respected history in both medical ethics and the law. In the context of providing hormones and surgeries to gender-dysphoric minors who wish for these interventions, the advocates of medical interventions are misrepresenting the nature of patient autonomy.

109. Rather than the right to *demand and receive* any treatment, patient autonomy is rightfully understood as the patient's right to *consent to* and to *refuse* treatment. Medical care cannot be done without a valid informed consent. It cannot be provided against the patient's will. The court stated this clearly in *Schloendorff v Society of New York Hospital*:

> *"Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages."* [75]

110. Patient autonomy has never meant that a patient or their guardian have the right to *demand and receive* treatment that is inappropriate or harmful. For example, pediatricians routinely decline to provide antibiotics to children with viral infections. Well-meaning and deeply concerned parents may be looking for, and even demand, antibiotics as a solution to a child's viral illness. However, we do not prescribe antibiotics in these cases because they have no role in viral infections, carry risks to the child, and the inappropriate use of antibiotics create resistance in the community. Likewise, when worried parents implore physicians for a CT scan of their child's head following a minor head trauma, a conscientious physician will decline such a request. There is no benefit to imaging for

[75] Schloendorff v. Society of New York Hospital, 1914 https://biotech.law.lsu.edu/cases/consent/schoendorff.htm

minor head trauma and there are well-recognized risks that are not insignificant, including sedation and radiation exposure. In these cases, we are not "denying care." We are providing the patients with appropriate medical care and safeguarding them from the risk of harm.

111. Like antibiotics for viral infections or CT scans for minor head injuries, puberty blockers, cross sex hormones, and surgeries do not have proven psychological or physical health benefits for gender-dysphoric youth. This lack of benefit has been the conclusion of recent quality systematic reviews by the UK, Sweden's, and Finland's public health authorities.[76,77,78,79] Sweden's National Health and Welfare Board has determined that risks of gender affirming care "currently outweigh the benefits." [80]

112. The medical risks of "gender-affirming" interventions are substantial. The most recent evidence shows that a gender-dysphoric child with normally timed puberty who is started on puberty blockers has a nearly 100% chance of continuing to cross-sex hormones.[81,82,83] This medical sequence will render the child sterile.

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[76] https://web.archive.org/web/20220414202655/https://arms.nice.org.uk/resources/hub/1070905/attachment

[77] https://web.archive.org/web/20220215111922/https://arms.nice.org.uk/resources/hub/1070871/attachment

[78] SBU. *Hormonbehandling Vid Könsdysfori - Barn Och Unga [Hormonal Treatment of Gender Dysphoria - Children and Adolescents]*. SBU; 2022. https://www.sbu.se/342

[79] Pasternack I, Söderström I, Saijonkari M, Mäkelä M. Lääketieteelliset menetelmät sukupuolivariaatioihin liittyvän dysforian hoidossa. Systemaattinen katsaus. [Appendix 1 Systematic Review]. Published online 2019:106. Accessed May 1, 2022. https://app.box.com/s/y9u791np8v9gsunwgpr2kqn8swd9vdtx

[80] https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2022-3-7799.pdf

[81] Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. *The Journal of Sexual Medicine*. 2018;15(4):582-590. doi:10.1016/j.jsxm.2018.01.016

[82] Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. Santana GL, ed. *PLoS ONE*. 2021;16(2):e0243894. doi:10.1371/journal.pone.0243894

[83] Brik T, Vrouenraets LJJJ, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. *Arch Sex Behav*. 2020;49(7):2611-2618. doi:10.1007/s10508-020-01660-8

113. Other medical harms also ensue. These include harms to bone health, cardiovascular health, brain development, and other problems. [84,85,86]

114. A physician who grants a minor's wish for these interventions is not respecting patient autonomy. That physician is misusing the principle of patient autonomy to justify unethical experimentation on minors.

115. Another key ethical dilemma regarding patient autonomy is whether the wishes of the 13-year-old should be privileged over the wishes of the future adult self. Can the 13-year-old self fully and truly know what the 25-year-old self will desire regarding the questions of sexual function and reproductive rights? We do not know what the 25-year-old will say about the loss of sexual function or fertility. A price may be paid that can never be recouped, all for bodily change that may or may not comport with the 25-year-old's future identity and desires.

116. It is a well-known fact that many adult trans-identified individuals choose not to undergo "gender-affirming" procedures that threaten their sexual function. While adults chose to preserve their fertility and sexual function, children at Tanner stage 2, which can occur in females as young as 8, are asked to contemplate, decide, and then consent to treatments with puberty blockers followed by cross sex hormones, which will cause sterility. Fertility

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[84] Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(2):E270-E275. doi:10.1210/jc.2014-2439

[85] Alzahrani T, Nguyen T, Ryan A, et al. Cardiovascular Disease Risk Factors and Myocardial Infarction in the Transgender Population. *Circ: Cardiovascular Quality and Outcomes*. 2019;12(4). doi:10.1161/CIRCOUTCOMES.119.005597

[86] Schneider MA, Spritzer PM, Soll BMB, et al. Brain Maturation, Cognition and Voice Pattern in a Gender Dysphoria Case under Pubertal Suppression. *Front Hum Neurosci*. 2017;11:528. doi:10.3389/fnhum.2017.00528

preservation – harvesting of egg or sperm – may be discussed by the proponents of medicalization. However, there are no mature egg or sperm to harvest at Tanner stage 2. Sterility is guaranteed with oophorectomy and removal of testes (castration).

117. It is important to note that a number of individuals who identified as transgender in their teen years and no longer identify as transgender upon reaching maturity have expressed gratitude that they did not undergo medical and surgical interventions that would have rendered them infertile. This sentiment is echoed by detransitioners who did receive these interventions and express disappointment, grief, and anger that nobody resisted their desires. No one challenged them. No one slowed down the younger version of themselves.[87,88]

118. The principle of patient autonomy also requires a fiduciary, trusting relationship between physician and patient. Truthfulness and full disclosure of information must occur for the patient and parent to exercise autonomy. As my arguments demonstrate, the low-quality evidence, lack of long-term follow-up, and increasing reports of harm, regret, and detransition, all raise grave concerns about "gender-affirmative care."

119. In my experience of having reviewed informed consent forms, speaking to physicians and therapists involved in "gender affirmative" care that refer for or prescribe puberty blockers and cross sex hormones, and talking to patients and parents who have transitioned or are seeking to transition, many of these concerns are not disclosed to patients and families. While some well-established risks are mentioned, the profound uncertainties are not acknowledged, and even denied by proponents of "gender-affirmative" care.[89]

[87] *See* Vandenbussche (2021)
[88] *See* Littman (2021)
[89] *See* Levine, 2022

120. For example, puberty blockers are often misrepresented as fully reversible despite mounting evidence that they irreversibly impeded bone growth, impact cognitive development, change the psycho-sexual profile toward a diminished sexual desire, and likely have a host of other yet unknown consequences. The relative safety record of puberty blockers administered for precocious puberty (e.g., a 5-year old who is starting to develop pubic hair and develop breasts) is being misrepresented as evidence that this intervention will be safe and fully reversible when used off-label to stop normally-timed puberty.

121. Puberty is the developmentally appropriate time when every organ system benefits from sex hormones to reach its optimal adult function. We do not know the long-term effects of stopping the biologically vital, normally timed process of puberty for several years. This is the reason why the UK's National Health Service recently replaced its statement that puberty blockers are reversible and now states: [90,91]

> "*Little is known about the long-term side effects of hormone or puberty blockers in children with gender dysphoria*." (NHS)

122. Also, it is typically not disclosed to the patients that the population on which the Dutch protocol was originally tested does not match most of the cases presenting today and that most cases treated with the protocol today would have been disqualified by the original study. Specifically, the Dutch excluded from transition adolescents whose transgender identity was not clearly established in early childhood, and those with significant mental

[90] https://www.spectator.co.uk/article/the-nhs-has-quietly-changed-its-trans-guidance-to-reflect-reality
[91] https://www.nhs.uk/conditions/gender-dysphoria/treatment/#:~:text=Puberty%20blockers%20and%20cross%2Dsex%20hormones&text=Little%20is%20known%20about%20the,the%20psychological%20effects%20may%20be.

health problems. [92] Nor is it typically disclosed to the patients and parents that the mental health of the Dutch study participants did not statistically or meaningfully improve after gender reassignment. Instead, these treatments are misrepresented as "life-saving."

123. Finally, patient autonomy is correctly understood as the freedom to act towards one's objective good. "Gender-affirming care" leads to sterilization, increased risk to general health (bone, cardiac, others), surgical complications, the potential for worsened mental health, and in a growing number of instances, future regret. These outcomes are objectively bad.

124. Thus, it is my opinion as a bioethicist that "gender-affirming" interventions with hormones and surgery for minors not only fail to support the core principle of Autonomy, but they directly violate it.

B. The principle of "Justice" is violated when minors are provided with "gender-affirming" hormones and surgery

125. The right to control one's reproduction and sexual function is well recognized by United States law and court rulings. Article 16 of the United Nations Universal Declaration of Human Rights recognizes that "men and woman of full age have the right…to found a family."

126. It is now well recognized that puberty blockers followed by cross sex hormones are, in effect, chemical castration, which is likely irreversible. The removal of testicles, which WPATH supports as early as 17 years of age in the draft of its upcoming guidelines, is irreversible castration.

[92] *See* Delemarre-van de Waal & Cohen-Kettenis, 2006 and Cohen-Kettenis et al., 2008.

127. It is unjust and unethical to sterilize a gender-non-conforming, mentally distressed adolescent. In my opinion, this is precisely what "gender-affirmative care" is doing to children. Children and adolescents do not have the capacity—the knowledge, understanding, and judgement—to comprehend the gravity of the decision they are making regarding their fertility.

128. The United States medical profession has a shameful history regarding forced and coerced sterilization of minors and adults without informed consent. All people of goodwill now agree that the court erred when it upheld these unethical sterilization practices in Buck v Bell (274 U.S. 200, 1927). [93]

129. It is my opinion as a bioethicist that "gender-affirming" interventions for minors violates the core ethical principle of Justice.

C. The ethical principles of "Beneficence" and "Non-Maleficence" are violated by providing minors with "gender-affirming" hormones and surgeries

130. The principles of beneficence and non-maleficence are fundamental principles of medical ethics. They require that medicine must do good and avoid harm. The Dutch Study[94] on which the practice of pediatric transition rests (as evidenced by the Endocrine Society Guidelines' citations [95]) has demonstrated that the "good" was narrowly defined and remains highly uncertain, while the "harm" was self-evident.

131. The Dutch Study claimed the greater "good" by claiming (correctly) that post-surgery the young adults who emerged after transition were functioning well, or even better, than the

[93] https://supreme.justia.com/cases/federal/us/274/200/

[94] *See* de Vries et al., 2014

[95] *See* Hembree et al., 2017

average 21-year-old Dutch peer. However, the study authors did not reflect on the fact that their screening methods nearly guaranteed such an outcome, since their carefully-selected 70 study subjects were already extremely high functioning before treatment.

132. Their beneficial claims also fail to address the harm to the patient with postoperative death after genital surgery and several instances of diabetes and obesity that developed during treatment.[96]

133. It has been longer than 10 years since these adolescents were transitioned, and we have no long-term follow up on this cohort. However, another study by the Dutch of an adolescent treated with the same protocol several years earlier did follow that individual into their mature adult years and the results are not reassuring. When this individual was first followed as a young 20-year old shortly after surgery, he was happy with the transition and the appearance of his genitals.[97] However, when followed up again at the age of thirty-five the situation had changed.

134. The patient was living alone and unable to form a loving relationship with a partner. He attributed the inability to form a long-lasting stable relationship to the shame about his genitalia. [98] This case does not lend confidence to the notion that the youth in the Dutch Study will be thriving in key aspects of their lives once they reach a mature adult age.

135. The Endocrine Society relies heavily on the Dutch Protocol in writing their guidelines, yet they fail to address the serious harms that were present and reported in the Dutch Study.

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[96] *See* de Vries et al., 2014

[97] Cohen-Kettenis PT, van Goozen SHM. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *European Child & Adolescent Psychiatry*. 1998;7(4):246-248. doi:10.1007/s007870050073

[98] Cohen-Kettenis PT, Schagen SEE, Steensma TD, de Vries ALC, Delemarre-van de Waal HA. Puberty Suppression in a Gender-Dysphoric Adolescent: A 22-Year Follow-Up. *Arch Sex Behav*. 2011;40(4):843-847. doi:10.1007/s10508-011-9758-9

They fail to mention or address the fact that fertility was destroyed in 100% of the youth transitioned in the Dutch Study. Nor are the 3 cases of new onset diabetes and obesity that developed during the Dutch Study addressed by the Endocrine Society. It cannot be said for certain that transition caused these effects, but a 4.3% rate of diabetes in a pediatric population is highly unusual and should lead to further concern and study. Another adolescent in the Dutch Study stopped short of gender confirming surgery. This patient has had irreversible changes from puberty blockers followed by cross-sex hormones. We do not know the effects of these permanent changes on this young person's life.

136. The one young person who tragically died as a result of surgical complications has already been mentioned. Death was due to tissue necrosis as a complication of a vaginoplasty: a procedure to construct a neo-vagina from the penis after castration. This translates into a 1%-2% death rate.

137. The evidence of regret is now emerging from newer research. The first large study of detransitioners in 2021 reported on 237 people. They stopped transitioning on average 4 years after starting. [99] Another study of 100 people who regretted their sex transition stopped the process on average 3.9 years after it began.[100] These numbers dwarf the participants in the Dutch Study, which ended their report 18 months after transition.

138. Many of the studies that purport benefit of transition recruit participants from online pro-transition activist sites. [101,102] At the same time, little attention is paid to the emerging

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[99] See Vandenbussche, 2021.

[100] Littman, 2021

[101] Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2):e20191725. doi:10.1542/peds.2019-1725

[102] D'Angelo R, Syrulnik E, Ayad S, Marchiano L, Kenny DT, Clarke P. One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Arch Sex Behav*. Published online October 21, 2020. doi:10.1007/s10508-020-01844-2

online communities of detransitioners and their stories are readily dismissed by proponents of affirmative care. One such community has over 28,000 subscribers, at least half of whom are estimated to be actual detransitioned patients.[103] The sheer numbers of people on the site sharing their devastating transition stories, their regret, and their harms dwarfs the Dutch case series of 55. The stories posted here are heart wrenching and indisputable evidence of the great harm being done.

139. There is no doubt in my mind that parents of children receiving "gender-affirming" interventions want the best for their children, and they are acting on advice of professionals. It is the physicians and counselors whom I believe have failed these parents and their children, falsely asserting that gender transition will help their children long-term. Many of these professionals themselves are misled by the activism that has taken over US-based professional bodies.

140. No matter how well-meaning the advocates of pediatric gender transition are, their actions lack beneficence. The experiment of medically and surgically transitioning minors lacks long-term outcome data. There is no meaningful evidence of long-term benefits. There are many demonstrable harms. And there remain many unknowns and uncertainties.

D. True informed consent for "gender-affirming care" for minors is not possible

141. Informed consent is another foundational principle of bioethics. It rests on all the other principles and requires a trusting and truthful relationship with one's physician. Physician-patient relationships must respect personal autonomy, promote the patient good, avoid harms, and seek justice. As a bioethicist, I am deeply concerned that valid informed

[103] https://www.reddit.com/r/detrans/

consent, a prerequisite of ethical care, is not possible in the context of "gender-affirmative care" for minors.

142. For informed consent to be valid the minor child or parent must understand the proposed procedure. The possible benefits, risks, limitations, and alternatives must be disclosed to the minor patient and parent. Since the information regarding "gender-affirmative care" is of low quality, unreliable, and very uncertain, a true understanding is not possible.

143. Also, for the consent to be valid, alternative approaches, including the approach to not medically intervene with one's gender non-conformity, must be discussed. However, alternative approaches such as psychotherapy,[104] which are now recommended as the first line and often the only treatment for gender dysphoric youth in European countries, are often withheld from US children and misrepresented as "conversion." This is dishonest and further undermines the informed consent process.

144. In addition, informed consent is not valid if decisions are made under coercion or duress (The Nuremberg Code, 1946).[105] It is highly problematic that the so-called "gender specialists" raise the specter of suicide. This can only alarm parents and their children, with wrongful and unsupported claims that these radical interventions are "lifesaving." These claims wrongly imply that transgender patients will commit suicide if not permitted to transition.

145. It is true that self-harm and suicidal thoughts are increased in trans-identified youth, but the suicide risk is on par with youth who have other mental health conditions, and thankfully,

[104] Schwartz D. Clinical and Ethical Considerations in the Treatment of Gender Dysphoric Children and Adolescents: When Doing Less Is Helping More. *Journal of Infant, Child, and Adolescent Psychotherapy*. Published online November 22, 2021:1-11. doi:10.1080/15289168.2021.1997344

[105] https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial/nuremberg-code

the absolute risk of suicide among gender-dysphoric youth remains exceedingly rare, recently estimated at 0.03% over 10 years in the UK.[106] That the US is not doing similar quality research with clinic-referred populations, instead relying on alarmist statistics derived from online activist surveys, further emphasizes just what an outlier the US-based approach to gender dysphoric minors has become compared to the rest of the western world.

146. Unfortunately, no study to date has been able to demonstrate that actual suicides are reduced post-transition. Parents are wrongly and unethically told that transition is the only solution to their child's problems. The "transition or suicide" mantra proclaimed by gender ideology is coercive, untrue, and unethical. [107]

147. Ethical behavior demands that we are truthful with our patients. Dishonesty, deceit, and coercion are unethical. Problematically, in my experience, some proponents of medicalization of minors mislead children and their families that "gender-affirming care" leads to a "sex change." They assert that through the hormonal and surgical manipulations of one's physical body, the "true sex," which they claim is signified by their "gender identity" will be allowed to emerge. I have heard from youth who decided to detransition when they finally come to the realization that they will never become the opposite sex. It is hard for me to believe that professionals mislead children in such a fundamental way.

148. Children believe adults. This is especially true when adults with medical degrees assure them that they can change sex. At least some of these children will be bitterly disappointed later when they realize that they will be medically dependent for life. Cross-sex hormones

[106] Biggs M. Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom. *Arch Sex Behav*. Published online January 18, 2022. doi:10.1007/s10508-022-02287-7

[107] https://www.wbez.org/stories/id-rather-have-a-living-son-than-a-dead-daughter/69b0e784-d9c1-44a3-a0f7-419864fe0d3c

will be needed for life to maintain the superficial appearance of the desired sex. They will never be able to procreate. Their sexual function destroyed, and reproductive capacity lost forever. And they will come to realize that their sex, which permeates every cell in their body, is immutable and unchangeable.

149. Mature adults with well-controlled mental health problems can consent to gender transition, provided they have received full and truthful disclosure of the complete range of benefits, risks and uncertainties associated with gender transition.

150. However, I am confident that children are not capable of either consenting or assenting to such a profound decision under any circumstances—and especially when they and their caregivers are effectively being misled by the medical community in fundamental ways.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on May 1, 2022.

Patrick Hunter

CURRICULUM VITAE

Patrick K. Hunter, MD, MSc

PERSONAL DATA

Place of Birth	Chicago, IL
Home Address	[redacted]
Telephone	[redacted]
Email	[redacted]

EDUCATIONAL DEGREES

May 1992	MD	University of Louisville Louisville, Kentucky
April 2020	MSc, Biomedical Ethics	University of Mary Bismarck, ND
May 1988	BA Zoology	Miami University Oxford, Ohio

POSTGRADUATE TRAINING

1992 to 1995	Internship and Residency Tripler Army Medical Center Department of Pediatrics Honolulu, Hawaii

PROFESSIONAL EXPERIENCE

January 2022-present	Pensacola Pediatrics Milton, FL
August 2015 to December 2021	Lake Nona Pediatrics, in Association with Nemours
August 2013 to July 2015	The Maui Medical Group Wailuku, HI Member, Board of Directors
June 2008 to June 2013	U.S. Department of Defense Tripler Army Medical Center and Naval Health Clinic Hawaii Honolulu, HI Academic General Pediatrician Chief, Mother-Baby Unit
July 1998 to June 2008	The Purcell Clinic Laurinburg, North Carolina Partner/Owner
July 1995 to June 1998	Staff Pediatrician & Chief of the Pediatric Clinic Captain, Medical Corps US Army Darnall Army Community Hospital Fort Hood, Texas

CURRICULUM VITAE

Patrick K. Hunter, MD, MSc

EDUCATIONAL APPOINTMENTS

July 2017 to present	Assistant Professor of Medicine University of Central Florida College of Medicine
March 2009 to June 2015	Assistant Clinical Professor Department of Pediatrics University of Hawaii John A. Burns School of Medicine
February 2012 to July 2013	Assistant Clinical Professor Department of Pediatrics Uniformed Services University of the Health Sciences Bethesda, Maryland
1998 – 2008	Study Investigator North Carolina Children and Adult Research Foundation

CLINICAL INTERESTS

Biomedical ethics
Judicious use of health care services
Immunizations
Asthma -- patient and parental education and motivation
Promotion of early childhood literacy
Newborn and Neonatal Care
Breastfeeding Promotion
Infectious Diseases
Well Child Care
Motivational Interviewing

HOSPITAL APPOINTMENTS

Nemours Children's Hospital Orlando, FL	2015 to 2021
Ethics Committee	
Maui Memorial Hospital Wailuku, HI	2013 to 2015
Tripler Army Medical Center Honolulu, HI	2008 - 2012
Scotland Memorial Hospital Laurinburg, NC	1998-2009
Medical Record Review Committee	2001-2002
Chairman, Department of Pediatrics	2001-2002, 2007-2008
Medical Executive Committee	2001-2005, 2007-2008
Medical Staff Secretary	2001-2002
Chief of Staff—Elect	2002-2003
Chief of the Medical Staff	**2003-2004**
Chair, Credentials Committee	**2004-2005**
Physician Effectiveness Committee	**2002-2008**

CURRICULUM VITAE

Patrick K. Hunter, MD, MSc

MEDICAL LICENSES

Hawaii
Florida

BOARD CERTIFICATION

American Board of Pediatrics — October 1995

COMMUNITY SERVICE

Scotland County Habitat for Humanity
Board Member — 2002-2003

Scotland Memorial Hospital
Foundation Board Member — 1999-2002

Scotland Memorial Hospital
Board Member — 2003-2005
Executive & Operating Committee Member — 2003-2004

St. Andrews Presbyterian College
Laurinburg Area Campaign Committee — 2000 and 2007

St. Anthony Catholic Church
Knights of Columbus — 2008 to 2013
Pastoral Council — 2010 to 2012

St. Thomas Free Clinic — 2018 to 2021
Pediatrician

St. John Fisher Catholic Church — 2018 to 2021
Finance Committee

ABSTRACTS, PAPERS, AND PRESENTATIONS

The Western Society of Pediatric Research Annual Meeting, February 1994
Pallister Hall syndrome in siblings, a case report and review of the literature Abstract and presentation

Smith AE, Vedder TG, Hunter PK, et al. The Use of Newborn Screening Pulse Oximetry to Detect Cyanotic Congenital Heart Disease: A Survey of Current Practice at Army, Navy, and Air Force Hospitals. *Military Medicine*. March 2011; 176(3) 343-346

Hunter PK. Political Issues Surrounding Gender Affirming Care of Transgender Youth. *JAMA Pediatrics*. December 2021; 176(3):322-323. doi:10.1001/jamapediatrics.2021.5348

DOC. 69-7

DEFENDANT'S EXHIBIT 7

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER, *et al.*,	)	
Plaintiffs,	)	
v.	)	No. 2:22-cv-00184-LCB-SRW
KAY IVEY, in her official capacity as Governor of the State of Alabama, *et al.*,	)	
Defendants.	)	

DECLARATION OF DIANNA KENNY

My name is Dianna Kenny. I am over the age of 19, I am qualified to give this declaration, and, I have personal knowledge of the matters set forth herein.

I am a former Professor of Psychology at the University of Sydney. I now practice as a consulting psychologist and psychotherapist. My CV is attached to this declaration. Recent publications can be found at www.diannakenny.com.au and https://www.researchgate.net/profile/Dianna-Kenny. Some are also listed on my CV.

I was retained by the State of Alabama as an expert witness in the above-styled case. A copy of my expert report is attached to this declaration. It contains my opinions in this matter based upon my research and experience. I have reviewed the Complaint filed by the Plaintiffs and the declarations submitted by the Plaintiffs.

In the past four years, I have provided expert testimony in the following cases: 12, supplied on request.

I am compensated at the rate of $__400__ per hour for my work on this matter. My compensation is not dependent upon the substance of my opinions or the outcome of the case.

Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct. Executed on ___1 May__, 2022.

Dianna Kenny

IN THE UNITED STATES DISTRICT COURT

FOR THE MIDDLE DISTRICT OF ALABAMA

NORTHERN DIVISION

JEFFREY WALKER, et al.,

Plaintiffs,

v.

STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama, BRIAN C.T. JONES, in his official capacity as District Attorney for Limestone County, and JESSICA VENTIERE, in her official capacity as District Attorney for Lee County,

Defendants.

Civil Action No. 2:22-cv-00167

DECLARATION OF DIANNA KENNY PHD IN SUPPORT OF

S.B. 184 (THE "FELONY HEALTH CARE BAN" OR THE "BAN")

TABLE OF CONTENTS

CHAPTER 1

SOCIAL CONTAGION

Abstract

In this chapter, I review the evidence for social contagion of gender dysphoria in adolescents. I begin with a review of the historical phenomenon of social contagion, demonstrating that it predated the digital age. I then review the nature of social contagion and the mechanisms by which certain phenomena are propagated through social networks. Social network analysis, the method applied to study contagions of all kinds, was first developed and used in public health as a way of determining the spread of diseases. For the spread of social phenomena among adolescents, three mechanisms - peer contagion, deviancy training and co-rumination in peer groups - have been identified as "spreaders." Four possible causes of peer effects – endogenous, exogenous, correlated and social media – all amplify the spread of information in a social network. Four areas of empirically established social contagion in adolescents - marijuana use, eating disorders, non-suicidal self-injury, suicide and emotion – are presented as a prelude to the discussion of how the same processes are at work in the social contagion of gender dysphoria and the wish to transition in adolescence. Specific mechanisms of transmission such as low gender typicality, peer victimization, ingroups, the trans-lobby, the role of social media in rapid onset gender dysphoria (ROGD) in are proposed. Preliminary statistical support for social contagion in gender dysphoria are presented.

INTRODUCTION: SOCIAL CONTAGION PREDATES THE DIGITAL AGE

> It is not famine, not earthquakes, not microbes, not cancer but man himself who is man's greatest danger to man, for the simple reason that there is no adequate protection against psychic epidemics, which are infinitely more devastating than the worst of natural catastrophes - Carl Jung

The term social contagion describes the "spread of phenomena (e.g., behaviours, beliefs and attitudes) across network ties" (Christakis & Fowler, 2013, p. 556). Social contagion has existed long before the advent of the digital age and social media. In 1774, Johann von Goethe (1990) published a novel, *The sorrows of young Werther*, in which an idealistic young man finds his actual life too difficult to reconcile with his poetic fantasies, including his

unrequited love for his friend's fiancée. He eventually becomes so depressed and hopeless by the perceived emptiness of his life, he commits suicide. Goethe was able to capture the nameless dread and endless longing of the human condition so well that his novel spawned a number of suicides, committed in the same way that Werther had killed himself, by shooting (Phillips, 1974). Such was the alarm created by this phenomenon, the book was banned in several European cities.

More than two hundred years later, in 1984, the suicide of a young Austrian businessman, who threw himself in front of a train, initiated a spate of similar suicides that averaged five per week for nearly a year. Sociologists argued that this alarming occurrence was amplified by media coverage that glamorised suicide by providing graphic images of the suicidal act and details of the young man's life. When media exposure of the event was curtailed and then stopped completely, the suicide rate dropped by 80 percent almost immediately. Although the influence of suggestion and imitation on suicide rates was dismissed by Durkheim (2005/ 1897), Phillips's (1974) work indicated that these factors do indeed play a significant role in the increase in suicides following a publicised suicide.

In 1841, a Scottish journalist, Charles Mackay (2012) wrote a book entitled *Extraordinary popular delusions and the madness of crowds.* In the preface to the first edition of the book, the aim of writing it is stated thus:

> …to collect the most remarkable instances of those *moral epidemics* … to show how easily the masses have been led astray, and how imitative and gregarious men are, even in their infatuations and crime (p. 1) …Popular delusions began so early, spread so widely, and have lasted so long, that instead of two or three volumes, fifty would scarcely suffice to detail their history... The present may be considered…a miscellany of delusions, a chapter only in the great and awful book of human folly (p. 3).

The preface to the second edition in 1852 continued this theme:

> Nations… like individuals, …have their whims and their peculiarities; their seasons of excitement and recklessness… whole communities suddenly fix their minds upon one object and go mad in its pursuit; …millions of people become simultaneously impressed with one delusion, and run after it, till their attention is caught by some new folly more captivating than the first. At an early age in the annals of Europe its

> population lost their wits about the sepulchre of Jesus and crowded in frenzied multitudes to the Holy Land; another age went mad for fear of the devil and offered up hundreds of thousands of victims to the delusion of witchcraft... the belief in omens and divination of the future… defy the progress of knowledge to eradicate them entirely from the popular mind… *Men… think in herds; …they go mad in herds, while they only recover their senses slowly, and one by one* [Author's italics] (p. 7).

With the arrival of COVID-19, the World Health Organization (WHO) warned that there would be an "infodemic"[1] of misinformation spawned by social contagion. This has in fact occurred, but the false beliefs have not taken centre stage and swept all science before it in the manner of transgender ideology. As Anderson (2018)[2] concluded:

> The [transgender] movement has to keep patching and shoring up its beliefs, policing the faithful, coercing the heretics, and punishing apostates, because as soon as its furious efforts flag for a moment or someone successfully stands up to it, the whole charade is exposed. That's what happens when your dogmas are so contrary to obvious, basic, everyday truths. A transgender future is not the "right side of history," yet activists have convinced the most powerful sectors of our society to acquiesce to their demands. While the claims they make are manifestly false, it will take real work to prevent the spread of these harmful ideas.

SOCIAL NETWORK EFFECTS UNDERLIE SOCIAL CONTAGIONS

Using very large datasets (e.g., Framingham Heart Study) that have collected longitudinal data on original participants (Original cohort), as well as their children (Offspring cohort) and their children's children (Third generation cohort) and including their spouses, siblings, friends and neighbours, Christakis and Fowler have shown that social network effects, known as clustering, remain strong and can extend to those up to three degrees of separation from the original cohort. Such effects have been demonstrated across a large range of factors by different researchers using differing datasets. Examples include overweight/obesity, sleep patterns, smoking, alcohol abuse, alcohol abstention, marijuana use, loneliness, happiness, depression, cooperation, and divorce among others. It can be argued that the spread of

[1] W.H.O. Fights a Pandemic Besides Coronavirus: An 'Infodemic' - The New York Times (nytimes.com)
[2] The Philosophical Contradictions of the Transgender Worldview - Public Discourse (thepublicdiscourse.com)

gender dysphoria and transgenderism is underpinned by these now well-established mechanisms of social contagion in other human behaviours.

Social network analysis, the method applied to study contagions of all kinds, was first developed and used in public health as a way of determining the spread of diseases (e.g., influenza, HIV/AIDS) that resulted in pandemics. It was subsequently applied to the challenges of introducing changes and innovations in the health system (Blanchet, 2013). Its applications have since expanded with the advent of computers, the internet, mobile and smart phones, and social media. Members of a network play different roles in the dissemination of innovations. A small number will adopt early (i.e., early adopters). Some of these will become opinion leaders who are central to the network who contaminate their "peers" (homophily) who in turn will influence those others at different levels of the network.

There are three types of social networks; (i) egocentric (networks assessing a single individual); (ii) sociocentric (social networks in a well-defined social space, such as a hospital or a school); and (iii) open system networks (e.g., globalised markets, social media). Each network consists of nodes (members), ties (connections between nodes), and measures of centrality, density and periphery or distance between the nodes. Networks with high centrality are the most effective in disseminating information or innovation. A key example is the transactivist lobby that has achieved spectacular success in a short time in changing health care, educational practices and legislation related to transgender individuals. Other characteristics of networks include cohesion (number of connections within a network) and shape (distribution of ties within the network) (Otte & Rousseau, 2002).

First, I examine the concept of social contagion and the mechanisms by which it influences behaviour and attitudes. Then I review four adolescent behaviours that have been empirically revealed to be subject to social contagion. I then demonstrate that the same principles of social contagion apply to the increase of young people who believe that they are transgender and are consequently seeking irreversible medical remedies to assuage their gender dysphoria. Finally, I explore the social contagion (i.e., clustering) of medical practice with respect to treatment of gender dysphoria, the precipitous legislation appearing in its support, and changes to policy and practice in education and sport, despite our collective failure to

date to fully understand the phenomenon of gender dysphoria and its rapid, epidemic-like spread in the Western world.

THE MECHANISMS OF SOCIAL CONTAGION

(i) Peer contagion

Peer contagion is a form of social contagion, defined as a process of reciprocal influence to engage in behaviours occurring in a peer dyad that may be life-enhancing (e.g., taking up a sport, studying for exams, health screening, resisting engaging in negative behaviours, altruism) or life-compromising (e.g., illegal substance use, truanting from school, aggression, bullying, obesity). Peer contagion has a powerful socializing effect on children beginning in the pre-school years. By early childhood, the time spent interacting with same-age playmates frequently exceeds time spent with parents (Ellis, Rogoff, & Cromer, 1981). Further, characteristics of peer interactions in schools (e.g., aggression, coercive behaviours, mocking peers) are carried over into the home environment (Patterson, Littman, & Bricker, 1967). By middle childhood, gender is the most important factor in the formation of peer associations, highlighting the significance of gender as the organizing principle of the norms and values associated with gender identity (Fagot & Rodgers, 1998).

(ii) Deviancy training as a mechanism of social contagion

Different mechanisms of transmission of peer influence have been identified. Deviancy training, in which deviant attitudes and behaviours are rewarded by the peer group have a significant effect on the development of antisocial attitudes and behaviours such as bullying, physical violence, weapon carrying, delinquency, juvenile offending, and substance abuse (Dishion, Nelson, Winter, & Bullock, 2004). Aggression in adolescence becomes more covert and deliberate and takes the form of exclusion, spreading rumours, and suborning relational damage among an adolescent's friendship network (Sijtsema, Veenstra, Lindenberg, & Salmivalli, 2009). Interestingly, adolescents associated with peers who engage in instrumental aggression became more instrumentally aggressive, while those associated with peers who engaged in relational aggression became more relationally aggressive, demonstrating the specificity of the effects of peer contagion via the deviancy training.

(iii) Co-rumination as a form of social contagion

Another form of peer contagion in adolescence is co-rumination, a process of repetitive discussion, rehearsal and speculation about a problematic issue within the peer dyad or peer group that underlies peer influence on internalizing problems such as depression, anxiety, self-harm, suicidal ideation and suicide (Schwartz-Mette & Rose, 2012). Co-rumination is more common among adolescent girls (Hankin, Stone, & Wright, 2010) although a similar phenomenon among boys has been observed. Being in a friendship that engages in perseverative discussions on deviant topics has been associated with increased problem behaviour over the course of adolescence. The longer these discussions, the greater the association with deviant behaviour in later adolescence (Dishion & Tipsord, 2011).

Peer contagion may undermine the effects of positive socializing forces such as schools, rehabilitation programs for young offenders, and treatment facilities for eating disorders among others. Collecting same-minded adolescents into group programs may be counter-productive because the peer influence impacts of a homogeneous peer group to maintain disordered behaviours may be greater than the program effects of the treatment facility (Dishion & Tipsord, 2011).

Young people are particularly vulnerable to peer contagion if they have experienced peer rejection, hostility and/or social isolation from the peer group (Light & Dishion, 2007). On the contrary, protective factors against peer contagion effects include secure attachment to parents, adequate adult supervision and oversight of the young person's activities, school attendance, and the capacity for self-regulation (T. W. Gardner, Dishion, & Connell, 2008).

(iv) Social contagion has a causal effect on behaviour uptake

Establishing a causal role for the effect of peer behaviour on adolescents is difficult because adolescents choose their peer networks; that is, they choose to associate with like-minded adolescents and those exhibiting similar attributes (homophily). This raises the question: Do adolescents choose their peers because they sanction and engage in similar behaviours or can peer social networks explain the uptake of (new) behaviours in individuals in the network? Sophisticated statistical models have been used to tease out the relative contributions of peer selection and peer influence. Correctly attributing the effects of these two factors has

important policy implications since most interventions for reducing risky behaviour among adolescents are implemented at a school level (Ali & Dwyer, 2010).

(v) The special case of social contagion via social media

In the world of social media, social contagion takes on a new, less complex, and narrower meaning:

> "Unlike the broadcasts of traditional media, which are passively consumed, social media depends on users to deliberately propagate the information they receive to their social contacts. This process, called social contagion, can amplify the spread of information in a social network" (Nathan & Kristina, 2014, p. 1).

For example, the social network 'Instagram' is one of the most popular platforms for adolescents and young people, with 44% reporting Instagram to be an important part of their daily lives (Feierabend et al. 2015). Analysis of content shows that it is a major vehicle for the sharing of mental health issues, including depression, eating disorders, and non-suicidal self-injury (NSSI) (Fischer et al. 2015).

Systematic reviews have identified both potential risks and benefits of online activity. On the one hand, it reduces social isolation and offers encouragement, camaraderie, and reduction of self-harm impulses. On the other, it enables, enhances, or triggers potential risks of 'copycat' behaviours such as NSSI, suicide, and eating disorders through normalization of pathological behaviours, or vicarious and social reinforcement of these behaviours (Brown, et al., 2017).

A number of studies have demonstrated the impact that social media can have on emotional contagion. For example, one study[3] demonstrated that interactions with others can alter our mood in the direction of the mood of the person with whom we are interacting. A number of mechanisms - for example, social influence, social selection, and shared external causation – can impact our changes in mood. The phenomenon is prevalent in bounded social networks such as touring orchestras where adolescent musicians have been observed to become more

[3] Block, P., & Burnett Heyes, S. (2020). Sharing the load: Contagion and tolerance of mood in social networks. *Emotion*. Advance online publication. doi: https://doi.org/10.1037/emo0000952

reciprocally similar in mood to their close associates on tour. The observed emotional contagion effects are greater for negative than positive moods.

In a study on Twitter posts[4], the distribution of positive and negative comments varied according to weekends and holidays. Figure 1 shows the trends.

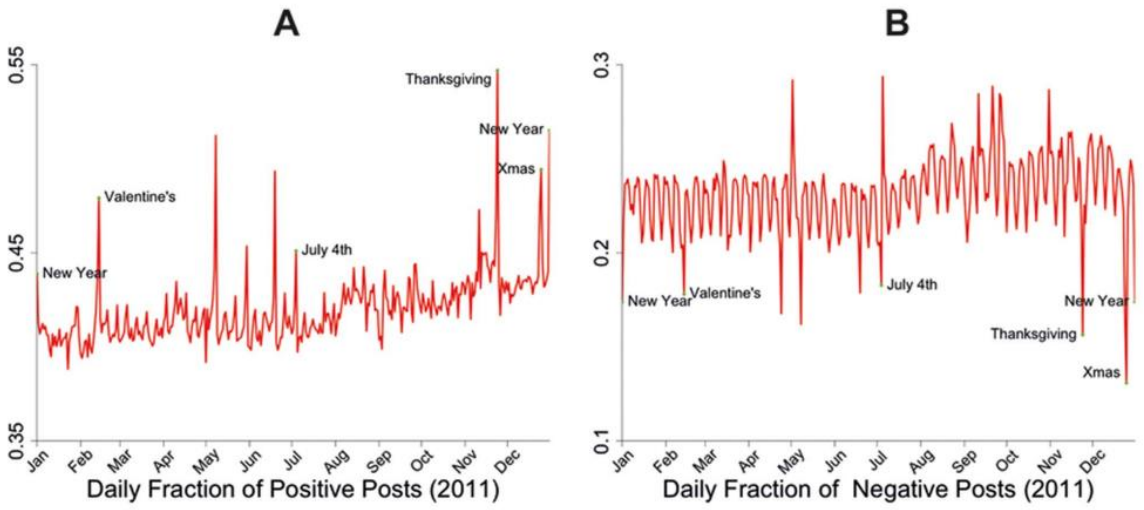

Figure 1

Pain behaviour has also been shown to be affected by the social mechanisms of observation, modelling, vicarious learning, social interaction and media reports. Both placebo and nocebo hyperalgesia have been recorded in patients who observed confederates modelling pain behaviour in response to social stimuli[5].

While many studies show how emotions spread between individuals in direct contact, a novel study demonstrated that online social networks produce emotional contagion in the same way[6]. Using data from millions of Facebook users, the researchers showed that rainfall directly influences the emotional content of their status messages, including messages of friends in other cities who were not experiencing rainfall. Results showed that …"for every person affected directly, rainfall altered the emotional expression of one to two other people,

[4] Golder SA, Macy MW (2011) Diurnal and seasonal mood vary with work, sleep, and daylength across diverse cultures. *Science* 333: 1878–81.
[5] Benedetti, F. (2013). Responding to nocebos through observation: social contagion of negative emotions. *Pain*, *154*(8), 1165.
[6] Coviello, L., Sohn, Y., Kramer, A. D., Marlow, C., Franceschetti, M., Christakis, N. A., & Fowler, J. H. (2014). Detecting emotional contagion in massive social networks. *PloS One*, *9*(3), e90315.

suggesting that online social networks may magnify the intensity of global emotional synchrony" (p. 1165).

EVIDENCE FOR SOCIAL CONTAGION AMONG ADOLESCENTS

In this section, I review the evidence for social contagion among adolescents for four key psychopathologies that arise in adolescence (eating disorders, marijuana use, non-suicidal self-injury, and suicide) and compare the mechanisms of social contagion in these well documented areas with evidence for social contagion in gender dysphoria.

(i) Anorexia nervosa

A number of researchers have identified the central role of social contagion in the development and propagation of anorexia nervosa in adolescent girls (Allison, Warin, & Bastiampillai, 2014). Adolescence is a time in which the focus on oneself becomes intense, and for some, critical and unrelenting. The developing female body constitutes one of the main objects of scrutiny. When this scrutiny is compounded by the collective inspection of all of one's body's flaws, the peer group becomes a powerful crucible for both the development and maintenance of disordered eating.

Intensification of peer influence in closed communities of like individuals, such as schools, inpatient wards, residential units (Huefner & Ringle, 2012), or therapy groups often results in the advocacy of the practices (e.g., self-starvation, compulsive exercise, deceitful practices around eating) associated with anorexia nervosa (Dishion & Tipsord, 2011).

If we add social media and online networks as further sources of influence, affected adolescents can effectively surround themselves exclusively with like minds, thereby normalising cognitive distortions around eating and body image and making recovery very difficult. These effects are further compounded by the high status of thinness in western culture, and an ubiquitous focus on nutrition and exercise. Originally thought to be caused by genetics and pathological family dynamics, this view was revised with the finding, using longitudinal study designs and social network analyses, that same-gender, mutual friends were most influential in the development of obesity in adulthood, with siblings and opposite-sex friends having no effect (Christakis & Fowler, 2007).

(ii) Marijuana use among adolescents

Substance use amongst adolescents is a major public health issue (Fletcher, Bonell, & Hargreaves, 2008), with a population study conducted by the Center for Disease Control and Prevention showing that 10 percent of youths reported using illegal substances before the age of 13, with marijuana the most frequently used substance (Chen, Storr, & Anthony, 2009). Peer influence has long been suspected as a stimulus that amplifies risky behaviours in the social network (Clark & Loheac, 2007; Lundborg, 2006).

Using the National Longitudinal Study of Adolescent Health (Add Health) (n=20,745) representing a sample of adolescents from grades 7-12 in 132 middle and high schools in 80 communities across the USA examined the influence of peer networks in the uptake and continued use of marijuana. The peer group was identified by the nomination of close friends and classmates within a grade were used to identify the broader social network from which friends were chosen (Ali et al., 2011).

Results showed that for every increase in marijuana use of 10 percent in adolescents in a close friend network increased the likelihood of marijuana use by two percent. An increase of 10% in usage in grade peers was associated with a 4.4 percent increase in individual use. Reporting a good relationship with one's parents, living in a two-parent household and being religious were protective against marijuana uptake. When peer selection and environmental confounders were held constant, increases in close friend and classmate usage by 10 percent both resulted in a five percent increase in uptake in individuals within those networks

(iii) Non suicidal self-injury (NSSI)

NSSI is defined as a deliberate self-inflicted attack on one's own body without suicidal intent. It excludes cultural practices such as ear piercing, tattooing, or circumcision, most of which are performed by others. NSSI is defined as socially contagious when at least two people in the same group inflict NSSI within a 24-hour time period. The social contagion of NSSI has been reported in a variety of 'closed' social networks such as in inpatient units, prisons, group homes, and special education schools, as well as in community samples of adolescents, young adults and college students (Jarvi, Jackson, Swenson, & Crawford, 2013).

Adolescence (onset between 12 and 14 years) and early adulthood are high-risk developmental periods for NSSI (Lloyd-Richardson, Perrine, Dierker et al., 2007). Between 14% and 21% of high-school aged adolescents report engaging in NSSI, with higher estimates (30%-40%) for adolescent psychiatric populations (Muehlenkamp, Hoff, Licht, Azure & Hasenzahl, 2008).

More recently, social media has been identified as an important conduit for social contagion of NSSI among young people. Platforms such as Instagram have high-frequency occurrences of pictures from adolescents who have self-harmed. When associations between characteristics of pictures (e.g., seriousness and type of the self-injury) and comments (e.g., supportive, empathic, negative, offers of help) and weekly and daily trends of posting were analyzed, patterns emerged suggesting social contagion. For example, the more serious injuries attracted more views and comments. Social reinforcement, imitation and modelling of NSSI through social media are the possible mechanisms whereby young people increase their risk of engaging in NSSI through digital means (Brown, Fischer, Goldwich, Keller, Young, & Plener, 2018; Fulcher, Dunbar, Orlando, Woodruff, & Santarossa, 2020).

(iv) Suicide

Although social ties are generally protective against loneliness, depression and suicide, social ties can be toxic and can amplify the risk of psychopathology in members of a social network (Christakis & Fowler, 2008). Exposure to the suicidal ideation or suicide attempts of significant others increases the risk of suicidality in other network members (Abrutyn & Mueller, 2014). Experiencing self-harm or suicide at close quarters may erode the emotionally regulating effects of normative moral precepts against such behaviour (Mueller, Abrutyn, & Stockton, 2015). When vulnerable individuals share “ecologically bounded spaces” (p. 205) like schools or the family home, this may increase suicide contagion if social relationships within those spaces are psychopathological. Our emotional connections to members of our social networks is the mechanism through which social learning and the development of normative behaviours and attitudes are built. However, negative emotions are more “contagious” and thus exert a greater impact on members (Turner, 2007).

Celebrity suicides also trigger spikes in suicide rates, with the greater visibility of the celebrity and prolonged coverage of the suicide triggering higher spikes and longer duration of

elevation of rates of suicide amongst fans (Fu & Chan, 2013; Stack, 2005). Durkheim (1951) highlighted the phenomenon of suicide outbreaks or "point clusters" defined as "temporally and geographically bounded clusters" such as gaols, regiments, monasteries, psychiatric wards, and First Nations reservations (Mueller et al., 2015, p. 206). Individuals in such networks share a collective identity that appears to heighten subsequent suicides following the suicide of the first decedent (Niedzwiedz, Haw, Hawton, & Platt, 2014).

Perhaps one of the most compelling studies on the social contagion of suicide is the study of celebrity suicides by Ha and Yang (2021). This study tracked the suicides 10 days before a well-publicised celebrity suicide and then the suicides 10 days after the suicide was reported in the media. Figure 2 presents these data graphically.

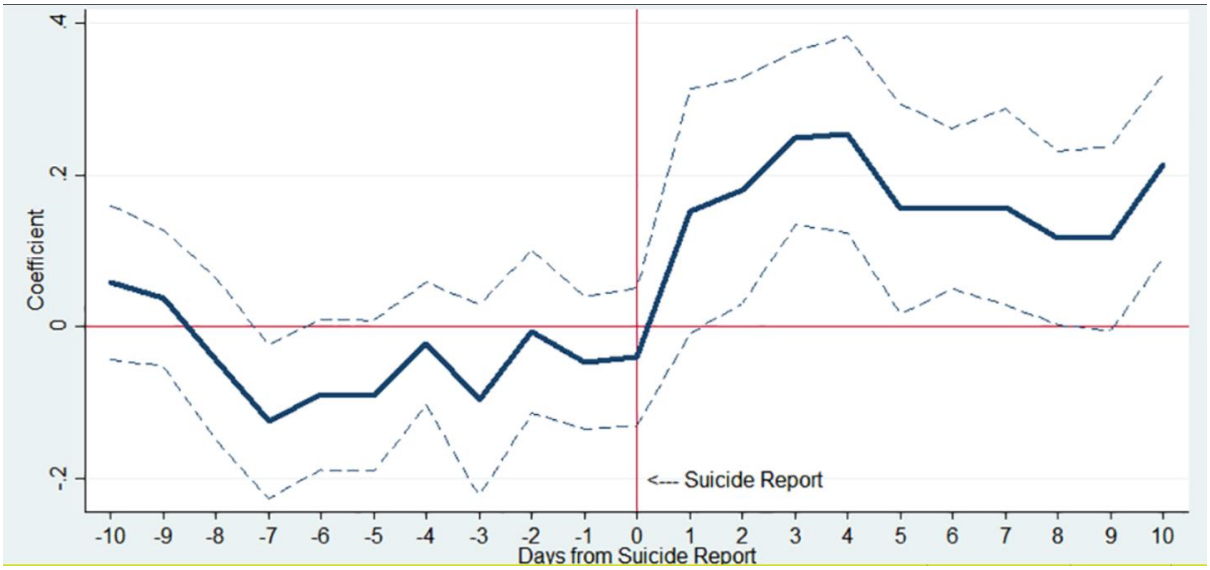

Figure 2[7] Suicide trends before and after reporting of a celebrity suicide

The sharp increase in suicides following celebrity suicide was mostly accounted for by suicides in the 10–29-year age group, the age group. Figure 3 shows the trends.

[7]The *y*-axis indicates an approximate percent change in public suicide by corresponding day

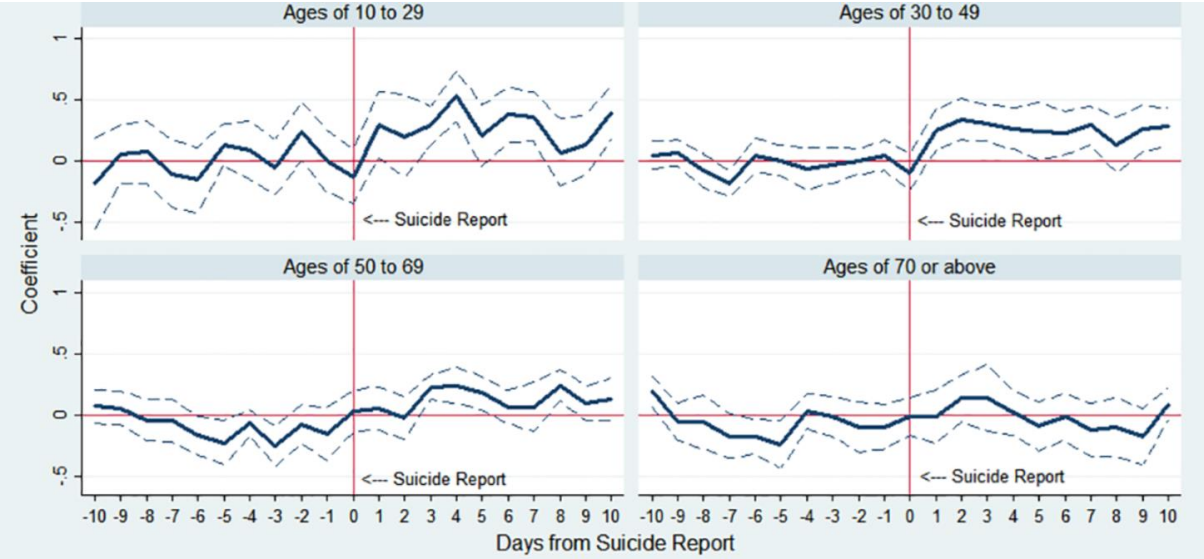

Figure 3 Suicide trends by age group

When the data are segmented by sex (Figure 4), the figures show that females are more susceptible to social contagion than males. The is exactly the same pattern of social contagion we are witnessing in gender dysphoria – young females aged between 10 and 29 years. Is this a coincidence?

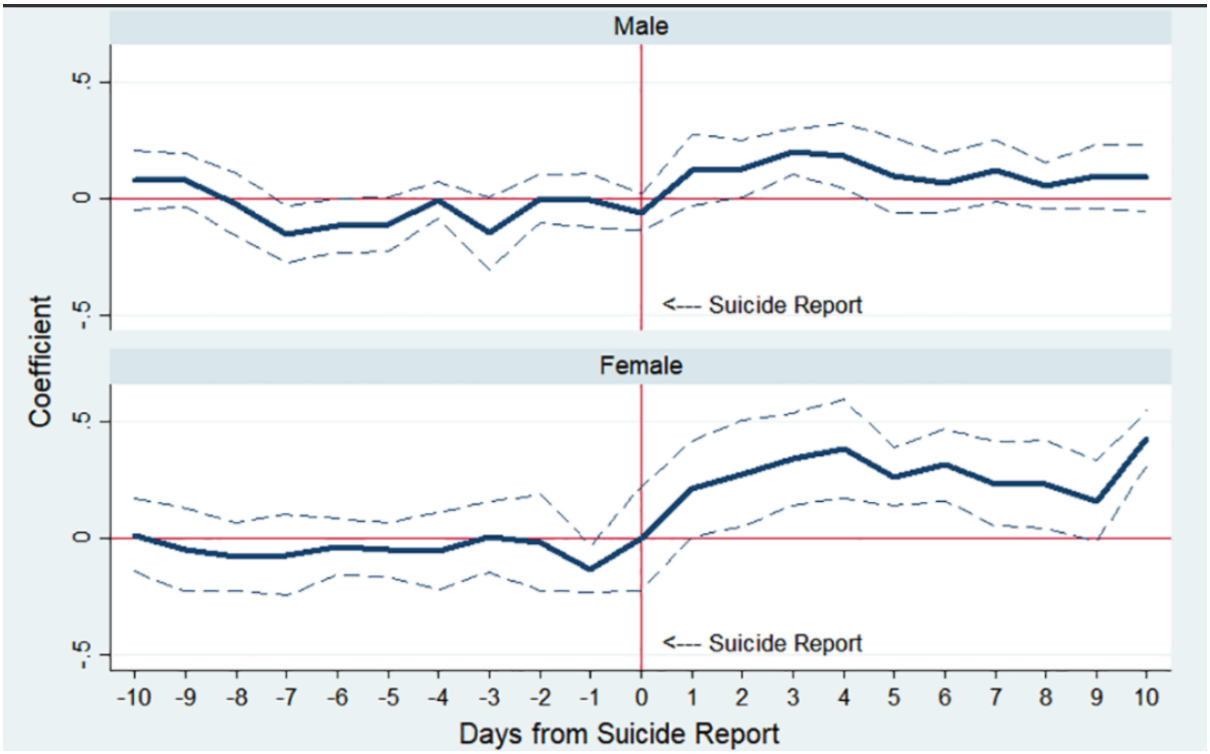

Figure 4 Suicide trends by sex

A well-documented example of a suicide "echo" cluster (an identical suicide cluster occurring within 10 years of a first cluster) occurred in two high schools in Palo Alto that, between them, had suicide rates four to five times higher than the national average. In 2009, three students committed suicide in a nine-month period by stepping in front of a commuter train. A fourth student committed suicide by hanging. In 2013 a mental health survey showed that 12 percent of students from these schools had seriously considered suicide in the previous 12 months. Thereafter, there was another spate of suicides, with three students taking their lives within three weeks of each other. A fourth committed suicide four months later by jumping off a tall building and a fifth followed shortly afterwards by walking in front of a train. Extreme perfectionism and pressure to excel at school, get into Stanford, make a lot of money, and be ostentatiously successful materially and intellectually were assessed to be far too great a burden for the more vulnerable students to withstand.

Using the same data set as the study examining marijuana use but following up four waves of these participants into adulthood, Wave IV assessed suicidality in young adults aged 24-32. This study showed that holding all other psychological risks constant, those young people having a role model who attempted suicide were more than twice as likely to report suicidal ideation in the following 12 months. Participants who had a friend or family member commit suicide were 3.5 times more likely to attempt suicide themselves compared with those who had no close associate attempt or commit suicide in the same 12-month timeframe. These effects were enduring. Young adults who reported an attempted suicide of a role model were more than twice as likely to report a suicide attempt six years after the role model's attempt compared with their otherwise similar peers. Attempting suicide in adolescence increased suicidal ideation and suicide attempts in young adulthood. Significant risk factors for this association included experiencing emotional abuse in childhood, a diagnosis of depression, and a significant other attempting suicide. Thus, suicide contagion appears to be a significant risk factor for suicide in young adulthood but contagion in this study did not require bounded social contexts.

SOCIAL CONTAGION OF GENDER DYSPHORIA

The UK has reported a 4,000% increase in the number of children presenting to gender clinics over the past 10 years. Similarly, Sweden has reported a 1,500% in the same time period.

Commentators on the burgeoning incidence of young people claiming that they are transgender assert that peer contagion may underlie this ominous trend. However, it has rarely been systematically studied either theoretically or empirically. Given the strong evidence of peer contagion in suicide, substance abuse and eating disorders, especially among adolescents, the role of peer contagion in gender dysphoria demands urgent attention.

If we examine the gender dysphoria epidemic in social network terms, we see several features operating. It is an open-system network with nodes and ties expanding across the oceans to the US, UK, Asia, Europe, Scandinavia, and Australia. Most countries are reporting sharp increases in the number of people seeking services and treatment for gender dysphoria. Many are ramping up services and setting up new gender clinics to cope with demand. This network is highly centralised with only one voice – the transactivist lobby - being heard above the desperate whispers of terrified parents and horrified academics, doctors, psychologists and psychotherapists. Opinion leaders operating at the centre of these networks are very influential. The level of density in a network has two effects – firstly, it enhances the circulation of information between members and secondly, it blocks the introduction of dissenting ideas and evidence (Iyengar, Van den Bulte, & Valente, 2011).

The field is too young to have attracted researchers to undertake social network analyses to assess peer contagion effects in gender dysphoria. Hence, formal empirical studies have not yet been conducted. However, there is evidence from several sources that peer contagion may be a relevant factor in the sharp increases in young people presenting with gender dysphoria.

(i) Low gender typicality, peer victimization, ingroups and the trans-lobby

Low gender typicality (i.e., perceived lack of fit within one's binary gender) has a significant impact on social acceptance within one's peer group (Sentse, Scholte, Salmivalli, & Voeten, 2007). It is strongly associated with adjustment difficulties, behavioural problems, lower self-esteem, and increased internalizing disorders (e.g., anxiety, depression) (Smith & Juvonen, 2017). As children progress to adolescence, peer as opposed to parental acceptance becomes paramount. Peers therefore take over the role of gender socializing agents from parents (Blakemore & Mills, 2014). Adolescent peers tend to be critical of behaviours, dress,

mannerisms and attitudes that are not gender typical as a way of policing and reinforcing gender norms and respond with criticism, ridicule, exclusion and even intimidation of non-conformers (Zosuls, Andrews, Martin, England, & Field, 2016). Research shows that the problems accruing to low gender typicality are mediated by peer victimization and that reducing peer victimization may ameliorate these difficulties (Smith & Juvonen, 2017). Conversely, peer acceptance mediated the self-worth of gender non-conforming 12- to 17-year-olds (Roberts, Rosario, Slopen, Calzo, & Austin, 2013). Gender non-conformity and gender atypicality have also been associated with higher physical and emotional abuse by caregivers (Roberts, Rosario, Corliss, Koenen, & Austin, 2012). Mental health is difficult to sustain in the face of caregiver abuse and peer bullying and victimization (Aspenlieder, Buchanan, McDougall, & Sippola, 2009). Indeed, gender non-conforming and gender atypical youth are at higher risk of depression, anxiety and suicidality in adulthood (Alanko et al., 2009).

It is tempting to speculate that these groups of young people, searching for homophily (i.e., like peers) started to exaggerate their points of difference from their gender-conforming peers rather than to hide and minimize them to avoid being bullied and excluded. In so doing, they left the "outgroup" of nonconformers and formed an ingroup of extreme gender-nonconformers, transcending the gender barrier altogether and declaring themselves transgender. Suddenly, the discomfort and fear of not being gender typical becomes a virtue and rather than fearing the disapprobation of their peers, their open revolt in declaring themselves transgender is valorised by a politically powerful transactivist lobby. One would expect that gender atypical children who feel both internal and external pressure to be gender conforming would experience greater discomfort (Carver, Yunger, & Perry, 2003) and therefore be more susceptible to the message of trans activism.

Ingroups behave in stereotypical ways with respect to outgroups – they favour ingroup characteristics, assigning more positive attributes to its members and derogating outgroups in order to enhance the status of their ingroup (Leyens et al., 2000). It is not surprising, then, that members of the transgender ingroup exaggerate the characteristics of the "trans" gender they take on – becoming more "feminine" or "masculine" than heteronormative groups of cismen and ciswomen. Transactivist groups have proliferated and consolidated in a short time frame by exploiting the characteristics of ingroups and outgroups. For example, social

projection (i.e., the belief that other members of the group are similar to oneself) has been a powerful integrating process that simultaneously creates protection for its own members and distance from outgroup members, using the formula, "if you are not with us, you are against us" – those disagreeing with the ideology of the trans-lobby are labelled "transphobic" and publicly denounced.

(ii) Rapid onset gender dysphoria (ROGD) and the role of social media

The upsurge in rapid onset gender dysphoria (ROGD) tends to occur mostly in girls at around the age of 14 years, which is an age identified by developmental psychologists to be particularly susceptible to peer influence (Steinberg & Monahan, 2007). For example, a study of peer contagion for risky behaviours found that exposure to risk-taking peers doubled the amount of risky behaviour in middle adolescents, increased it by 50% in older adolescents and young adults, and had no impact on adults (M. Gardner & Steinberg, 2005). This group of young people were likely to belong to peer groups in which one or more of their friends had become gender dysphoric or transgender identified. Their coming-out announcement to parents also tended to be preceded by recent increases in their daughters' social media and internet usage. It is only a small step to understanding the social contagion of ROGD in this age group.

Lisa Littman (2018) canvassed the perceptions of parents who had children who displayed ROGD during or just after puberty. There were 256 respondents, of whom 83% had daughters, with a mean age of 15.2 years when they declared themselves transgender,41% of whom had previously expressed a non-heterosexual sexual orientation, and 62.5% of whom had received a diagnosis for a mental health disorder (e.g., anxiety, depression) or a neurodevelopmental disability (e.g., autism spectrum disorder). Thirty-seven percent (37%) of these young people belonged to peer groups with other members identifying as transgender. Parents also reported a decline in their child's mental health (47%) and relationship with parents (57%) after declaring themselves transgender. Thereafter, they preferred transgender friends, websites, and information coming from the transgender lobby.

An indicative case study was written up in an article for *The Atlantic* by Jesse Singal (2018), in which a 14-year-old girl decided she must be trans because she was uncomfortable with her body even after she restricted her food intake, was finding puberty uncomfortable, had

difficulty making friends, was feeling depressed and was lacking in self-confidence. Against this backdrop of woes, she came across MilesChronicles[8], the website of an omnipotent and histrionic transboy, now a young transman. Watching this video resulted in Claire pouring all her sadness and unease about herself into the "realisation" that she was really a "guy." Miles made transitioning appear easy and simple, was effusive in his praise of his new self and supportive of others to follow suit. This is a very common scenario reported by parents of teenage girls with ROGD.

Such websites, all easily accessible to vulnerable adolescents, can have a very persuasive effect on viewers. Recent studies show that contagion is enhanced when the influencer is perceived to have high credibility and reduced when the influencer is perceived to have low credibility. A similar effect is observed if the influencer belongs to an out-group or an in-group (Andrews & Rapp, 2014). Miles is the quintessential trans pinup icon with a "You can be just like me if you transition!" message.

Following YouTube posts and social media with respect to the transgender debate over the past few years, I have noticed that posts that depict young people struggling with their gender identity or questioning their decision to take puberty blocking agents and cross-sex hormones, or to undergo what is euphemistically called sex reassignment surgery are rapidly taken down so that only a homogenous message that matches the strident messaging of the transactivist lobby is on display in the ether.

A recent Swedish study[9] tracked referrals and attendances at gender clinics of young people following major media events related to transgender health care in 2019. One event was positive, and two media events [i.e., the airing of "The Trans Train and the Teenage Girls,"[10] a 2-part documentary series broadcast on April 3, 2019 (event 2), and October 9, 2019 (event 3)] determined as negative portrayed gender transition as dangerous and damaging. In the three months following one of the negative media events, referrals decreased by 25% overall – there was a 32% reduction in female referrals - and by 25% for young people aged 13-18

[8] MilesChronicles - YouTube

[9] Indremo, M., Jodensvi, A. C., Arinell, H., Isaksson, J., & Papadopoulos, F. C. (2022). Association of media coverage on transgender health with referrals to child and adolescent gender identity clinics in Sweden. *JAMA network open*, *5*(2), e2146531-e2146531.

[10] . Mission: Investigate. The trans train and the teenage girls. Tranståget och tonårsflickorna. Video in Swedish. Swedish Public Service Television Co. April 3, 2019. Accessed December 28, 2021. https://www.svtplay.se/video/ 21717158/uppdrag-granskning/uppdrag-granskning-sasong-20-avsnitt-12

years. On the contrary, increased positive media coverage of trans issues resulted in an increase in referrals to gender clinics[11].

Nonetheless, a statement released in August 2021 by the Coalition for the Advancement & Application of Psychological Science (CAAPS)[12] called for the elimination of the use of Rapid-Onset Gender Dysphoria (ROGD), "given the lack of rigorous empirical support for its existence," although this evidence abounds (see next section on empirical evidence). Deplorably, CAAPS did not see fit to question the exponential increase in the adolescent trans phenomenon, both in declarations and referrals to gender clinics across the globe[13] nor how these new referrals differed substantially in profile from previously recorded demographics of transgender young people along dimensions of age of onset, sex ratio, comorbid mental health issues[14] and clustering.

EMPIRICAL EVIDENCE

In recent decades, there has been an unmistakably sharp increase in the population estimates of young people identifying as transgender. A retrospective analysis[15] (Figure 5) of the pattern of referrals to gender clinics from 1976 to 2011 is instructive in demonstrating the shifting

[11] Pang KC, de Graaf NM, Chew D, et al. Association of media coverage of transgender and gender diverse issues with rates of referral of transgender children and adolescents to specialist gender clinics in the UK and Australia. JAMA Netw Open. 2020;3(7):e2011161. doi:10.1001/jamanetworkopen.2020.11161

[12] https://www.caaps.co/rogd-statement

[13]de Graaf, N. M., Giovanardi, G., Zitz, C., & Carmichael, P. (2018). Sex ratio in children and adolescent referred to the Gender Identity Development Services in the UK (2009–2016) [Letter to the Editor]. *Archives of Sexual Behavior, 47,* 1301–1304;

Frisén, L., Söder, O., & Rydelius, P. A. (2017). [Dramatic increase of gender dysphoria in youth]. Lakartidningen. Retrieved from http://lakartidningen.se/Klinik-och-vetenskap/Klinisk-oversikt/2017/02/Kraftig-okning-av-konsdysfori-bland-barn-och-unga/.

Kaltiala-Heino, R., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: Overrepresentation of natal girls with severe problems in adolescent development. *Child and Adolescent Psychiatry and Mental Health, 9,* 9.

[14] Aitken, M., Steensma, T. D., Blanchard, R., VanderLaan, D. P., Wood, H., Fuentes, A. … Zucker, K. J. (2015). Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *Journal of Sexual Medicine, 12,* 756–763.

Ashley, F. (2019). Shifts in assigned sex ratios at gender identity clinics likely reflect changes in referral patterns [Letter to the Editor]. *Journal of Sexual Medicine, 16,* 948–949.

Becker, I., Gjergji-Lama, V., Romer G., & Möller, B. (2014). Characteristics of children and adolescents with gender dysphoria referred to the Hamburg Gender Identity Clinic [German]. *Prax Kinderpsychol Kinderpsychiatr, 63,* 486–509.

Littman, L. (2018). Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLoS ONE, 13*(8), e0202330.

[15] Wood, H., Sasaki, S., Bradley, S. J., Singh, D., Fantus, S., Owen-Anderson, A., ... & Zucker, K. J. (2013). Patterns of referral to a gender identity service for children and adolescents (1976–2011): age, sex ratio, and sexual orientation. *Journal of Sex & Marital Therapy*, *39*(1), 1-6.

patterns of presentations of young people to gender clinics. The sample comprised 577 children aged 3-12 years and 253 adolescents aged 13-20 years. Prior to around 2000, the child referrals greatly exceeded referrals of adolescents. After that time, there was a steep and significant increase in adolescents. Also of interest is that the overall sex ratio of male to female children was 4.5:1 (boys:girls). For three-year-olds the ratio was 33:1 (boys:girls). The ratio dropped to 3.4:1 in the last cohort of children (2008-2011). The adolescent sex ratios were at parity but by 2008-2011 girls exceeded boys.

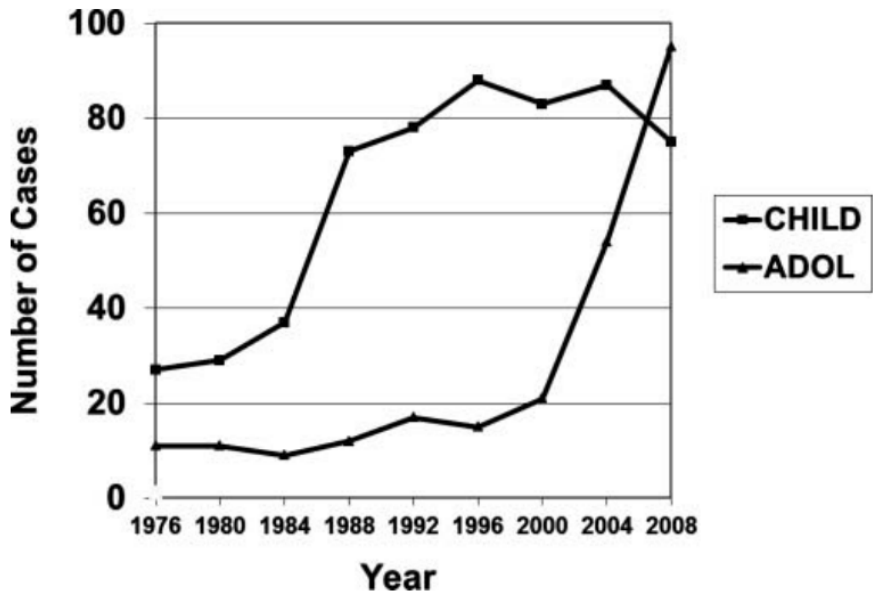

Figure 5 Number of children and adolescents referred to gender clinics 1976-2011)

For the adolescents in this study, data on sexual orientation were available for 248 participants. Using standardized measures[16] to assess heteroerotic and homoerotic sexual orientation in fantasy, 76% of the girls were classified as homosexual compared with 57% of boys. These figures vastly exceed population estimates of homosexuality and begs the question as to whether many young people presenting to gender clinics are confused about their sexual orientation, experience socialized and/or internalized homophobia or do not understand the difference between gender identity and sexual orientation.

[16] Zucker, K. J., Bradley, S. J., Owen-Anderson, A., Kibblewhite, S. J., Wood, H., Singh, D., & Choi, K. (2012). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex & Marital Therapy*, *38*, 151–189.

Another study, a meta-regression of population-based probability samples provides compelling evidence of this trend, where estimates have more than doubled in the space of eight years from 2007 to 2015 (See Figure 6).

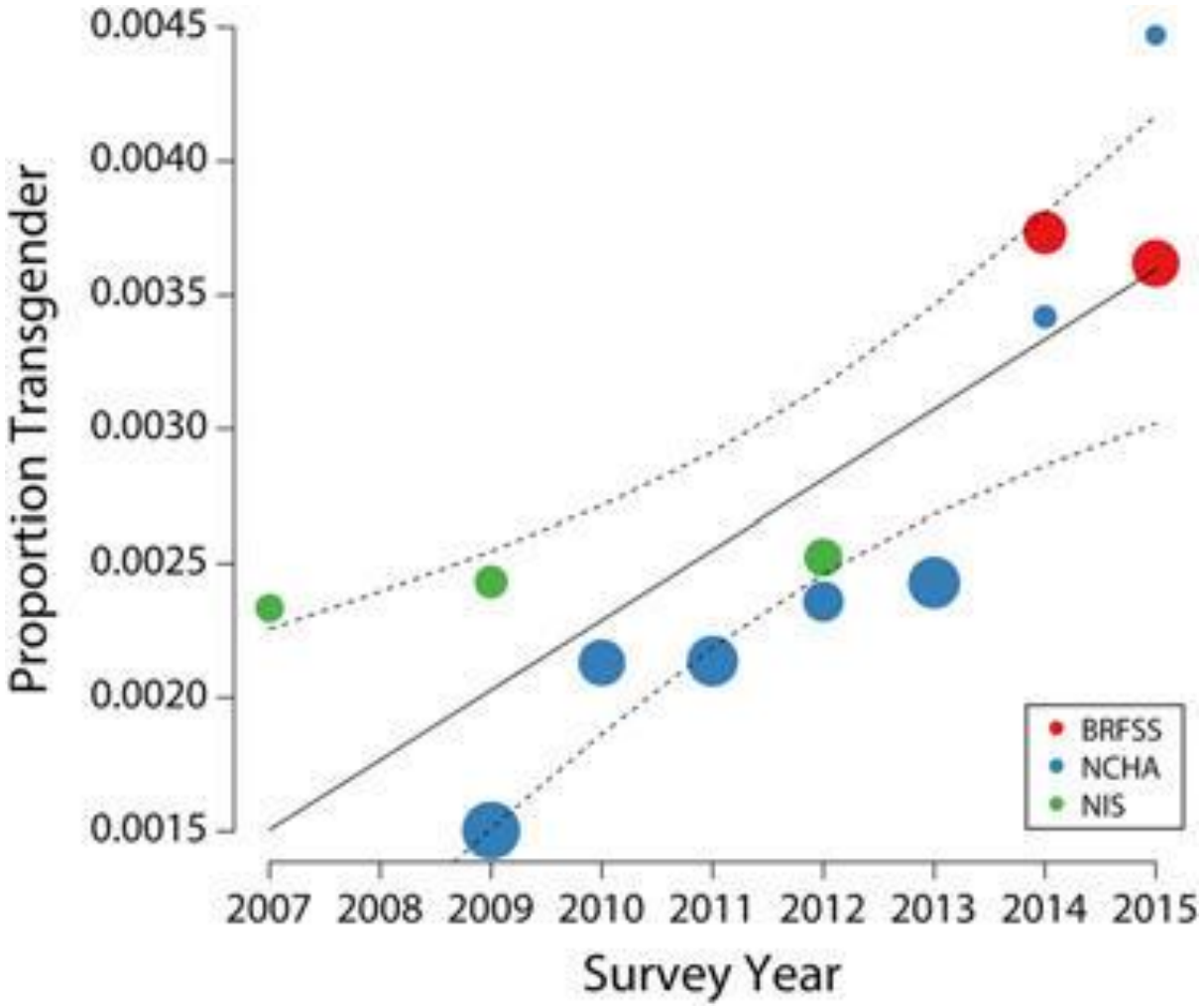

Figure 6[17] [Source: Meerwijk & Sevelius (2017)]

Similarly, upward trajectories of enrolments in GD clinics have been observed in the UK and Australia. Figure 7 summarizes the trends.

[17] Meerwijk, E. L., & Sevelius, J. M. (2017). Transgender population size in the United States: a meta-regression of population-based probability samples. *American Journal of Public Health, 107*(2), e1-e8. https://ajph.aphapublications.org/doi/pdfplus/10.2105/AJPH.2016.303578

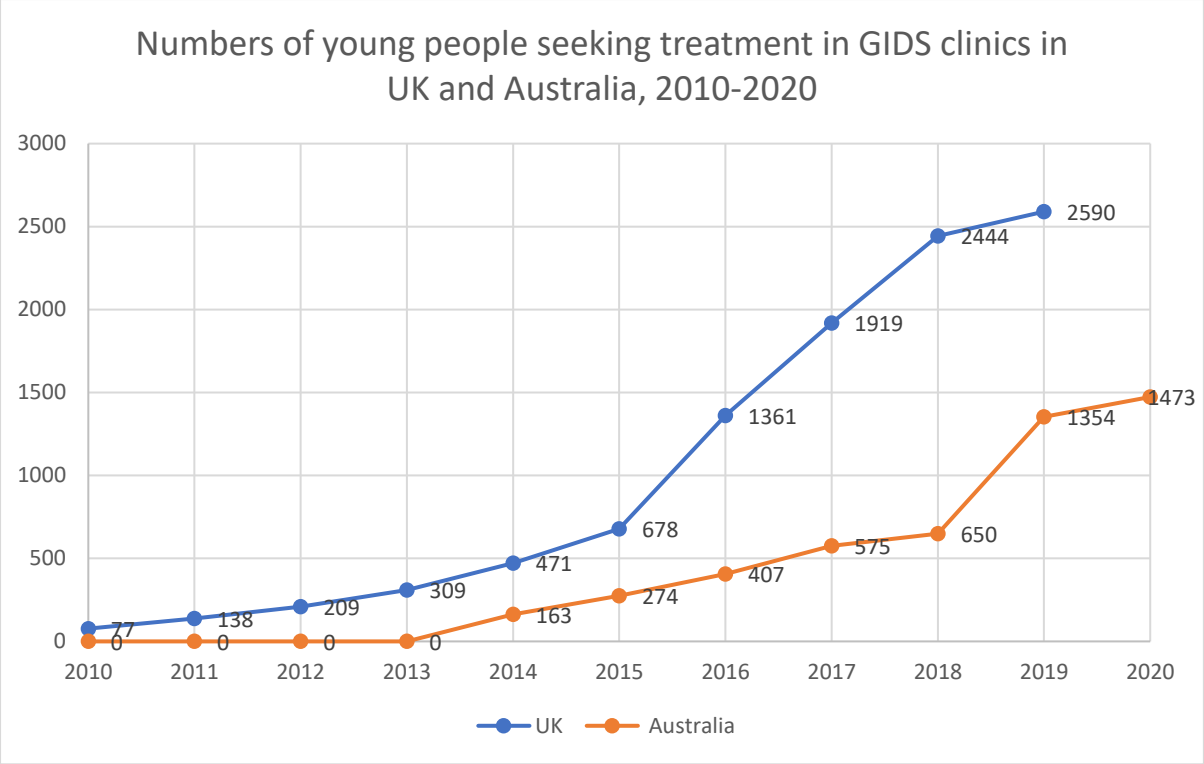

Figure 7

Source: Kenny, D.T. (2021). Australian data provided by the gender clinics under freedom of information applications

Perusal of the UK graph indicates a doubling of the number of referrals in 2015-2016 compared with the previous year. There is a continuous, but less steep increase until 2017, which is followed by a slowing of referral growth rates between the two years 2017-2018 and 2018-2019.

In each of these samples, these numbers would comprise two groups of young people, a core group of “actual” cases and the additional cases created by social contagion. Within the actual cases, there would be the group who declared themselves and a group of latently gender dysphoric young people who have not felt able to declare themselves until recently because of greater community acceptance and support from the transgender lobby and social media. This latter group of “actual” cases and the ROGD group have both been affected by social contagion.

Further analysis is required to determine the nature of the clustering of these increased numbers. In school-aged children, one would expect to see multiple cases in particular high schools. If gender dysphoria referrals occurred independently of each other, one would

expect to see referrals per high school follow a Poisson distribution, in which the variance is equal to the mean. A clustering effect would be hypothesised if the variance were greater than the mean. The strongest indicator of social contagion would occur if the ROGD young people showed strong clustering effects. Evidence that this may in fact be the case is provided by the distribution of new referrals by age and sex in the GIDS sample (Tables 2 and 3), where new referrals in the 12–16-year group far exceeds those in younger and older age groups.

Table 2 Age at referral to GIDS, UK in 2018-20

Age at referral	Number of referrals
3 and 4	10
5	21
6	21
7	42
8	34
9	43
10	59
11	78
12	135
13	331
14	511
15	529
16	474
17	88
18	30

Source: NHS (2019)

Age groups segmented by sex show much larger proportions of females seeking gender transition – for 13-year-olds, girls accounted for 86% of referrals, for 14-year-olds, girls accounted for 82% of referrals and for 15-year-olds girls accounted for 76% of referrals.

Table 3 GIDS figures from England by sex at birth

Age	2019-20, England only		
	Assigned sex at birth		
	AFAB	AMAB	Not Known
3 and 4	<5	<5	0
5	5	12	0
6	7	9	0
7	13	16	<5
8	17	24	<5
9	24	21	<5
10	22	32	0
11	52	23	6
12	127	37	5
13	270	45	11
14	404	90	16
15	470	152	31
16	350	162	24
17	101	67	10
18+	30	28	<5

Data from Australia (Figure 8) also show an upward trajectory in the number of children enrolled in gender clinics in the five states of Australia that offer a gender service over the period 2014-2020.

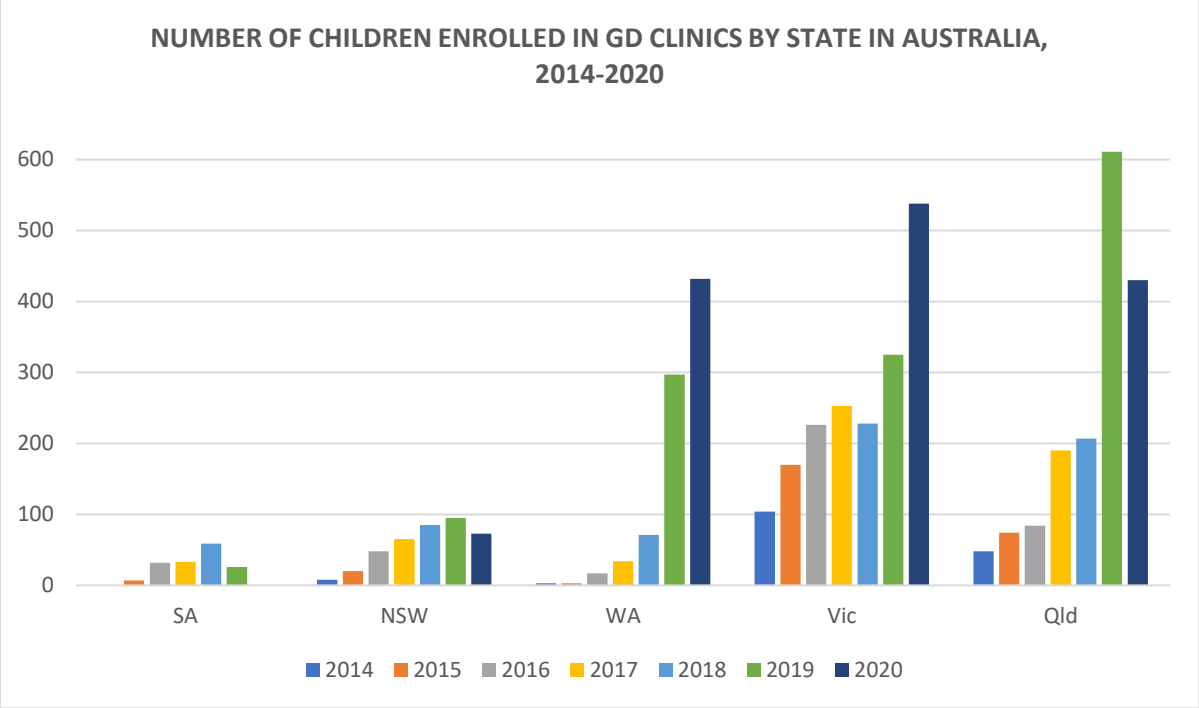

Figure 8

Source: Kenny, D.T. (2021). Data provided by the gender clinics under freedom of information applications

The noteworthy feature of this graph is that three states (WA, Queensland and Victoria) show similar increases over the five-year study period (2014-2020), although Queensland showed a downturn in 2020. While figures in NSW increased, the magnitude of absolute numbers was significantly lower than for the other states. Overall, Victoria had the largest numbers. It is also a state where the trans lobby has been particularly vocal, where the concept of the "safe schools" policy was conceived and implemented, and where the gender clinic at the Royal Children's Hospital, Melbourne has assumed the mantle of trailblazer in the gender transition enterprise in Australia.

Figures from the Nordic countries[18] show very similar patterns as those described above. See for example, Figure 9 below.

[18] Kaltiala, R., Bergman, H., Carmichael, P., de Graaf, N. M., Egebjerg Rischel, K., Frisen, L., ... & Waehre, A. (2020). Time trends in referrals to child and adolescent gender identity services: a study in four Nordic countries and in the UK. *Nordic Journal of Psychiatry*, *74*(1), 40-44.

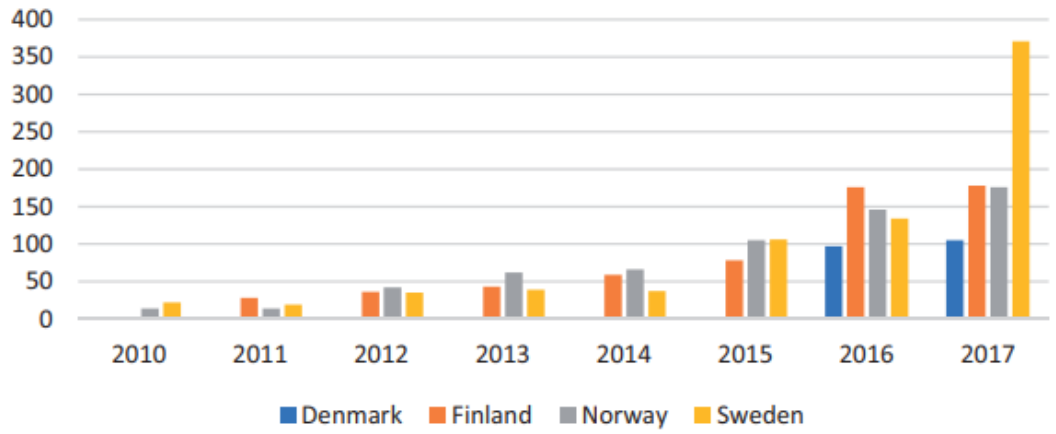

Figure 1. Referrals to child and adolescent gender identity services 2010–2017 in four Nordic countries.

Figure 9

Table 4[82] shows the dramatic increases in just a six-year time frame between 2011 and 2017 in the four Nordic countries and the UK (for comparison).

Table 1. Population adjusted numbers of referrals to gender identity services for minors in four Nordic countries and the UK in 2011 and 2017.

	2011	2017
Denmark[a]	–	9.0/100,000 (1/11,000)[c]
Finland	2.63/100,000 (1/38,071)[b]	16.7/100,000 (1/10,155)
Norway	1.24/100,000 (1/80,643)	15.6/100,000 (1/6414)
Sweden	0.90/100,000 (1/111,663)	17.4/100,000 (1/5719)
UK	1.25/100,000 (1/79,588)	17.5/100,000 (1/5078)

These population adjusted rates are orders of magnitude higher than those observed in transgender adult populations[19]. Rapid changes in any relevant biological factors that could possibly account for these trends across global populations appears both unlikely and implausible.

Figure 10[20] shows the total number of young people taking puberty blockers and cross-sex hormones over the seven-year study period across Australia.

[19] Zucker KJ. (2017). Epidemiology of gender dysphoria and transgender identity. *Sex Health,* 14(5):404–411.

[20] NSW supplied "0" in each data cell for each of the seven years. A follow-up inquiry to Sydney Children's Hospital Network (Ref No: SCHN18/7854, 6/8/19) indicated "Sydney Children's Hospitals Network (SCHN) does not provide cross sex hormones at The Children's Hospital at Westmead. [O]ccasionally SCHN sees a patient in a cross-over transition phase who has had stage two treatment initiated by an adult physician, as The Children's Hospital at Westmead pharmacy is still providing the patient's treatment in that cross-over phase. However,

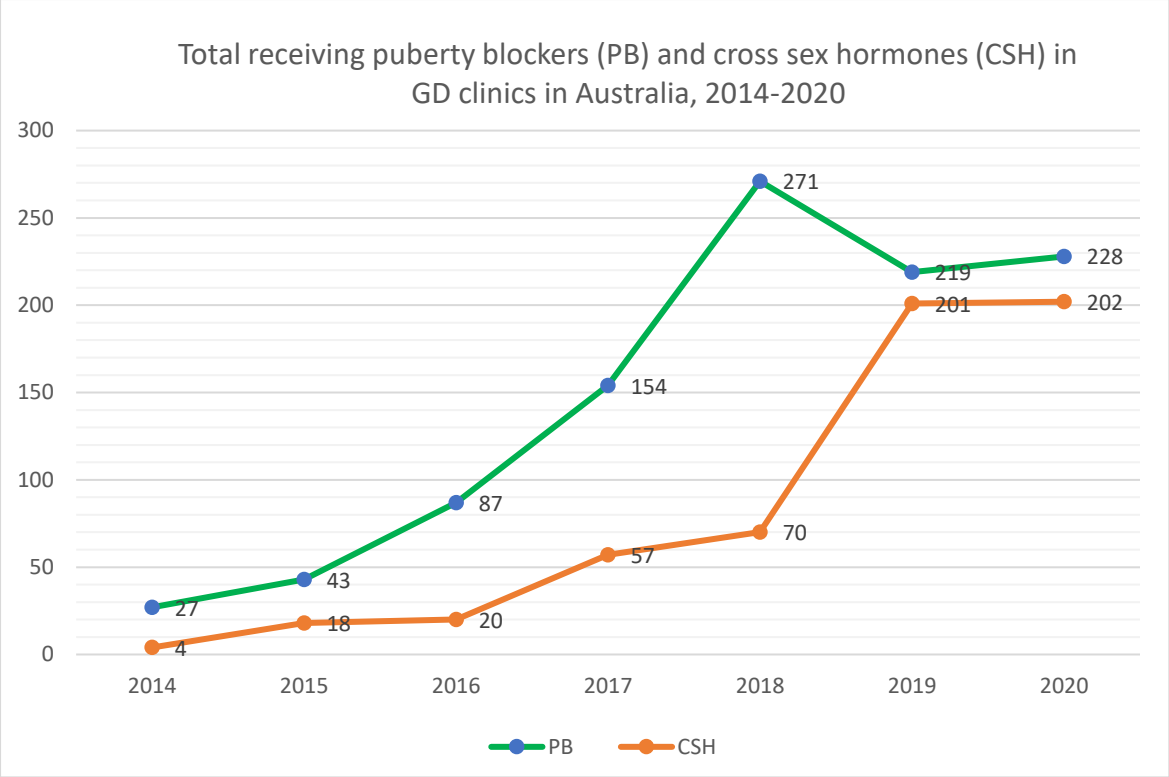

Figure 10

Source: Kenny, D.T. (2021). Data provided by the gender clinics under freedom of information applications

Finally, in case we are left in any doubt about why these numbers have been rapidly increasing over the past 10-15 years, Figure 11 shows the increase in the number of gender clinics across the USA in the past 15 years, from 2007 to 2022.

their primary care at this stage is under the adult physician who prescribes the stage two therapy. The zero-response provided in the GIPA Notice of Decision is correct but that there may be instances in which children are receiving active stage 2 treatment elsewhere while still attending The Children's Hospital at Westmead clinic".

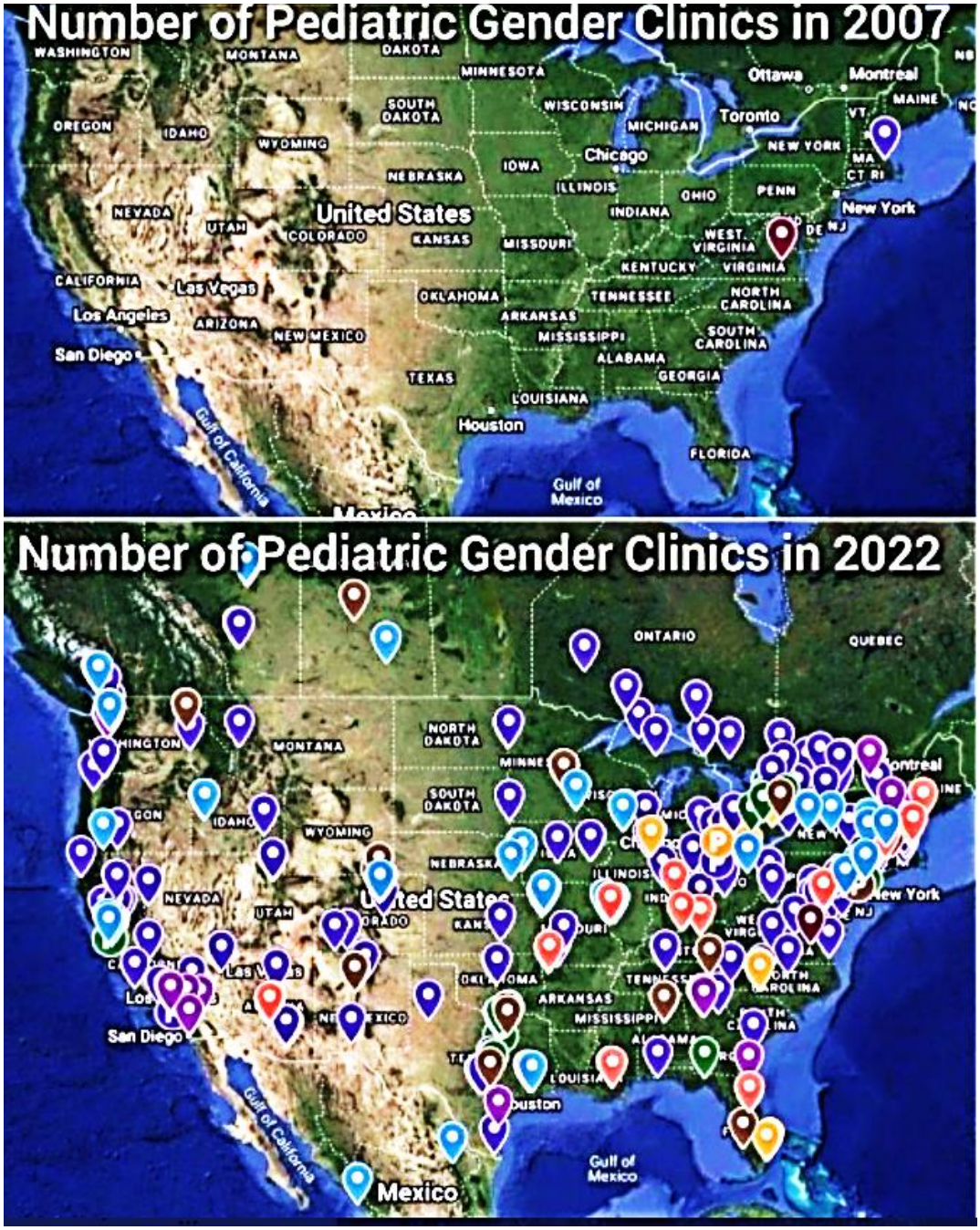

Figure 11 Number of gender clinics in USA and Canada in 2007 and 2022.

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CHAPTER 2

THERAPY FOR TRANSGENDER DECLARING ADOLESCENTS

Abstract

In this chapter, I present a detailed account of exploratory psychotherapy with an adolescent and a number of case studies of young people whom I have treated for gender dysphoria. Through respectful engagement, building of the therapeutic relationship and establishment of rapport and safety, these young people gradually reveal their developmental struggles and strivings, their complex and conflicted interpersonal relationships and growing understanding of their own intrapsychic process that will hopefully equip them to make informed decisions about their lives when they reach the age of majority. To deny young people the opportunity to engage in exploratory psychotherapy when they declare a transgender identity would risk exposing them to iatrogenic harm, which they may come to deeply regret. First, I present a detailed case study demonstrating how family, developmental history and social influences intersect in the formation of a transgender identity. I then present summaries of other cases to demonstrate how factors such as developmental psychopathologies and struggles with sexual orientation problematize young people's endeavours to understand themselves.

INTRODUCTION

The Cass Review[21] into the GIDS (Gender Identity Development Services) in the UK concluded:

> Primary and secondary care clinicians have reported to the Review that they are nervous about seeing children and young people with gender-related distress because of lack of evidence and guidance about appropriate management, and the toxicity of the societal debates. Some clinicians also reported feeling unable to undertake the process of assessment and differential diagnosis that would be the norm in their clinical practice because they perceived that there is an expectation of an unquestioning affirmative approach. They felt that this was at odds with a more open and holistic evaluation of the factors underpinning the young person's presentation, and consideration of the full range of possible support and treatment options.

[21] https://www.bmj.com/content/376/bmj.o629

The report also acknowledges that received medical wisdom about the treatment of young people with gender dysphoria is inappropriate and inapplicable to the young ROGD people currently presenting to gender services, in particular adolescent females who are now accepted to be influenced by the forces of social contagion. These include those with mental health issues, various forms of neurodiversity, and those from dysfunctional and disrupted families.

In a sample of 56 children appearing before the Family Court in Australia for permission to proceed to cross sex hormones, 25 of 39 cases in which family constellation could be discerned lived in single parent families or foster care, with only 14 from two parent families. In this same group of 56 children, 50% had a diagnosed psychological disorder, including six with autism spectrum disorder (ASD), major depression, anxiety, oppositional defiance disorder (ODD), ADHD, or intellectual disability. A recent study has shown a higher prevalence of gender dysphoria in those with ASD[22].

In a sample of 105 gender dysphoric adolescents and using the Diagnostic Interview Schedule for Children (DISC), anxiety disorders were found in 21%, mood disorders in 12.4%, and disruptive disorders in 11.4% of the adolescents. Males had greater psychopathology compared with females, including comorbid diagnoses[23].

Case studies from the public domain

In the early stages of attempting to understand young people identifying as transgender, I studied a large number of publicly available posts that young people had shared on the internet. Close reading of these scripts assisted my own theorizing about the psychodynamics of the transgendering process. Here are some examples:

Alex

Alex (a biological female), aged 12, petitioned the Family Court of Australia to permit her to transition. The Court made orders allowing the commencement of puberty-suppressing

[22] van der Miesen, A. I. R., Hurley, H., Bal, A. M., & de Vries, A. L. C. (2018). Prevalence of the wish to be of the opposite gender in adolescents and adults with autism spectrum disorder. *Archives of Sexual Behavior*. doi: 10.1007/s10508-018-1218-3

[23] 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, 52*(11), 1195-1202. doi:10.1111/j.1469-7610.2011.02426.x

hormone medication because of the intense distress Alex felt at her emergent feminine body. At 17, the Court granted permission for a double mastectomy. Psychiatric evidence indicated a traumatic childhood, in which Alex's mother rejected her completely. However, she had a close and idealised relationship with her father, who wanted her to be a boy and who treated her as such, even teaching her to urinate in the standing position. He died suddenly when Alex was six. Psychiatric evaluation revealed significant early trauma and concluded that "Alex's cross-gender identification appears to have emerged in the context of an idealised, physically close relationship with her father, rejection and abandonment by her mother, and her father's desire for her to be a male … Her investment as male simultaneously expresses anger towards her mother and maintains closeness with her dead father... in the context of her incomplete mourning for him"[24].

Ariel

Ariel, transfemale, aged 13, who had commenced puberty blockers, insisted on being called by the name of a different Disney princess every day, until she settled on the name, Ariel:

> I remember… when everyone was talking about having babies and it really makes me upset. I don't want to tell them to stop talking about it… but it hurts my feelings when they're talking about it… I am like a girl, but can I have the pain of labour? For a lot of people, it is hard for them to understand, but I don't want to burden them with that. Sometimes I just walk away and sometimes I try to get into the conversation, but it's hard". Her remarkably perceptive friend then says, "You can get so close to being a girl but you can't get to that exact point. Is that what upsets you?" Ariel says "Yeah, that's exactly how I feel, the thing with having a baby, I can never be fully there. It is a natural thing that happens. I buy a bra but it's not to hold in my boobs – it is an illusion. It felt like an act, so I feel lost sometimes[25].

Ariel articulates her lived experience of impersonating a girl rather than becoming one or being one. None of the culturally feminine ideals and products with which she surrounds

[24] Kissane, K. (2009). Young people, big decisions. Retrieved 21 May 2018, from https://www.smh.com.au/national/young-people-big-decisions-20090504-arxc.html

[25] (https://www.youtube.com/watch?v=sTfQ44HFu6k

herself can fully convince her that she is female. She acknowledges that it is an "illusion", "an act", and she feels "lost" that a true gender identity eludes her.

A transmale (unnamed)

A transmale, aged 13, had this to say about the role of the internet in his "coming out as trans":

> The internet is the best place for trans people, it is the best place you can go to if you are scared about talking to anyone. TUMBLR Oh, My God! TUMBLR! Youtube too. That's how I found out that I was trans – it was from a youtube video[26]…

This young person appeared to have no caring, empathic adult with whom to share his identity/gender confusion and turned to the internet to seek out like minds, that is, to find his "true" in-group. Seeking and finding membership in a valued in-group enhances self-esteem and feelings of belonging and affiliation (Buck, Plant, Ratcliff, Zielaskowski, & Boerner, 2013). Feeling alienated and marginalised in the "real" world, the virtual world of the internet appears to provide a substitute community missing in the child's real world. However, there is no opportunity to reality-test in such a process, and this young person may have commenced down a dangerous path in order to experience social inclusion. One can also characterize this process as social contagion, since it is likely that the transgender in-group comprise members who are also seeking inclusion and validation in an in-group. For another example of this process[27], in which a young boy says that the internet is "hugely important" particularly when parents are disapproving.

John

John, age 16, transmale,

> For as long as I can remember, I always felt male. I did come out to my parents as lesbian, sometime around seventh grade. I thought, "Oh well, I seem to wear boys' clothes all the time, I feel masculine, and I realise that I like girls, so then I thought, "OK, I must be a lesbian. That was tough. My dad, he wouldn't have any part of it. He said, "This is not a world that you are going to be a part of." Then, when I got to my

[26] https://www.youtube.com/watch?v=sTfQ44HFu6k
[27] https://www.youtube.com/watch?v=eYOuqgoxAik

> freshman year, I identified as trans, so I came out to them again as a transmale. I always had a hard time making friends. I was a very strange kid. I would just feel bad because every day I went to school, I felt like everybody wanted me to go; nobody wanted me there. One of the girls said, "Man, you are an ugly dyke. You are a lesbian." I went from shaky, to unstable, to almost impossible. I started drifting off to a very violent place in my head. I had thoughts of harming my family. It got so bad, I felt like a threat to my family, and to myself. One night, I went down to my mom and said that I wanted her to take me to a hospital; I wanted to get locked up.

This transcript demonstrates the confusion experienced by some young people with gender dysphoria as to their sexual orientation and gender identity, with some believing they are transgender when they are in fact homosexual/lesbian. Existing theories of transgender also conflate these two dimensions, based as they are on a "coming out" model developed for people with lesbian/gay orientations. There has also been a tendency to conflate gender identity with sexual orientation in seeking causal explanations[28].

From these and my own cases, I developed the following intake assessment.

INTAKE ASSESSMENT

A very careful intake assessment of every young person presenting with gender concerns needs to be undertaken. I have developed the following:

i. **Family constellation**, family conflict /dysfunction, marital and sibling dynamics

ii. **Trauma,** physical, emotional, and/or sexual abuse, attachment disorders

iii. **Psychological evaluation** – ADD/ADHD, ASD, learning disability, self-harm, suicidality, suicide attempts, anxiety, depression, incipient BPD, and psychosis

iv. History of **body dysmorphia**, eating disorders

[28] Katz-Wise, S. L., Budge, S. L., Fugate, E., Flanagan, K., Touloumtzis, C., Rood, B., . . . Leibowitz, S. (2017). Transactional pathways of transgender identity development in transgender and gender-nonconforming youth and caregiver perspectives from the Trans Youth Family Study. *International Journal of Transgenderism, 18*(3), 243-263.

v. **School life experiences** e.g., attitude towards school, peer rejection, bullying, truanting, academic performance, post school aspirations

vi. **Cognitive immaturity, concrete thinking, cognitive rigidity, and cognitive distortions**, lack of understanding or misunderstanding of gender ideology and capacity to critically review it (given the illogical and scientifically unsound basis of the ideology)

vii. Perceptions and misperceptions of **gender roles**

viii. **Degree to which there is understanding of the gravity and irreversibility of medical/surgical transition**; what gender affirmation treatment entails, and the consequences of treatment (e.g., infertility, sexual dysfunction, complications of cross-sex hormones and surgery, lifelong patienthood, relationship complexity).

ix. **Sexual experience** history – sexual relationships, sexual abuse experiences, sexual knowledge, sexual anxiety

x. Emerging awareness of **ego dystonic sexual orientation** - > internalized homophobia

xi. **Social contagion** (influence of social milieu e.g., schools, gender clinics, internet, online transgender communities)

xii. **Systemic function of ROGD** e.g., defiance of parents, finding an "in group," being "seen", denying the development of their sexed bodies, fear of adulthood, fear of sexual relationships.

Psychodynamic Formulation

Identity is not hard-wired – it develops in a social world where the young person experiences attachments, trauma, abuse, or misperceives the meaning of experiences because of cognitive immaturity or concrete thinking. Clinicians need to explore identifications (I want to be like…) and dis-identifications (I do not want to be like…) within the family, the peer group, and the social milieu.

The vulnerable (traumatized) part of the self is hated so it is subsumed into the omnipotent self which is the part that suppresses doubts and anxiety and presses for transition. If the traumatized self pushes for recognition of psychic pain, the young person may resort to self-harm and suicidal ideation which is a form of acting out of their self-

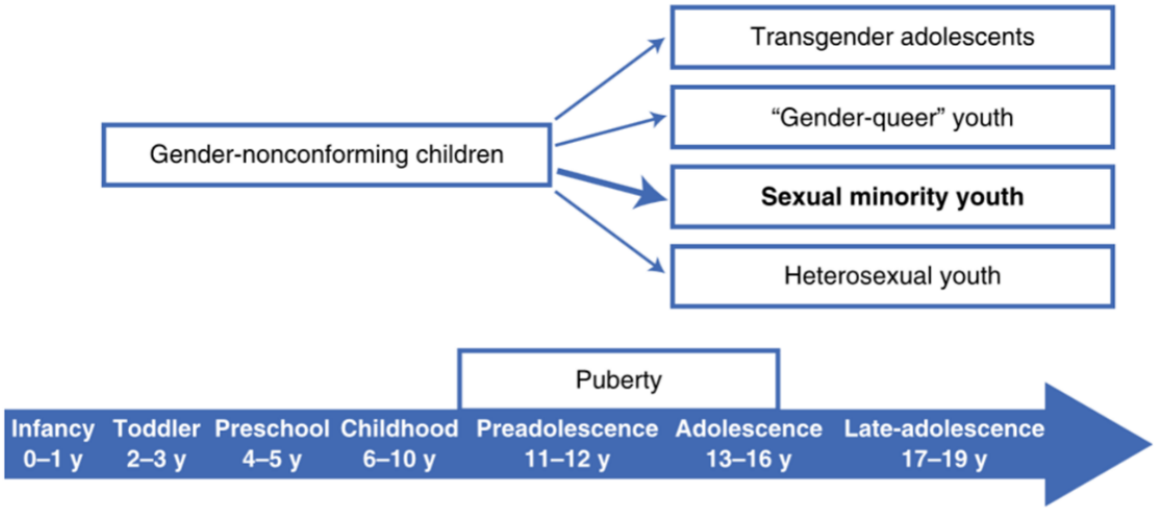
hatred against their bodies. Affirming clinicians collude with the patient's own attacks on the traumatized self by "traumatizing" their young patients' bodies with cross-sex hormones and mutilating surgery. In the hope that transition will restore the young person to an ideal state, medics become omnipotent creators of this ideal state. When this fails, the patient sinks into further self-hatred which is enacted through self-harming and suicidal states.

The majority of GD young people have had very limited life experience. For example, they

i. have had no sexual experience (other than crushes from a distance, hand holding and kissing)
ii. disdain genital sex as "gross"
iii. are indifferent to loss of sexual function and fertility, claiming that they never want to have children
iv. are confused about the nature of "trans" relationships e.g., a self-declared non-binary male (natal sex = male) in a relationship with a transgender declaring natal female (i.e., a trans man) told their parents they were in a gay male relationship. Similarly, two natal females, both transmen, rejected the suggestion that they were a lesbian couple and stated that they were a gay male couple.

It is imperative to keep the developmental path open into adulthood because frontal lobe maturation continues to occur into the early 20s. Further, there are several final trajectories for gender-nonconforming children. The trajectory of gender-nonconforming children varies greatly, and therefore, not all gender-nonconforming children will report persisting gender dysphoria once pubertal changes begin to develop. Prospective studies show that the majority of gender-nonconforming children will report being a sexual minority at some point later in life. An individual child's trajectory may not be known until later in life and it is imperative that this not be disturbed by iatrogenic interference[29].

[29] Leibowitz, S. F., & Telingator, C. (2012). Assessing gender identity concerns in children and adolescents: evaluation, treatments, and outcomes. *Current Psychiatry Reports, 14(2), 111-120*



Psychological trauma from the past forms part of one's psychic structure in the present. The expression of these traumas is socio-culturally embedded, that is, social contagion permits particular forms of "acting out" of these traumas. Envy and rivalry are an integral part of human condition; unconscious envy is a factor in trans identification. GD adolescents need assistance to explore their defences and internal psychic conflicts and to manage their psychic pain before irreparably altering their bodies. "The body is used to act out something that cannot be accepted or processed by the mind." (Evans & Evans, 2021, Ch 2, p. 28). Clinicians should not collude with the phantasy that the "embodied" self can be altered or removed.

Sexual development poses a threat to young people as it signifies approaching adulthood, the demands of which they feel ill equipped to manage. ROGD may be conceptualized as a "trauma" or a response to the reality of puberty that one now has a sexed body. Rigid adherence to peer norms temporarily assuages vulnerabilities because the young person has found others like him/her who are acting out in the same way. The desire for transition could be:

i. related to a grievance against the parents and a struggle for autonomy/individuation
ii. part of a process of identification and disidentification with parents and siblings
iii. related to an idea that one can create an ideal self
iv. protective against feelings of inadequacy, anxiety, jealousy, and disappointment
v. a triumph over feelings of vulnerability
vi. a repudiation of the sexed body and adulthood

DEVELOPMENTAL TRAJECTORIES OF YOUNG PEOPLE DECLARING THEMSELVES TRANSGENDER

Alicia

Alicia was a 14-year-old ROGD adolescent at the time of coming out as trans and starting therapy. She advised her parents that she was a trans male, whereupon they sought therapy for her. Alicia comes from an intact family and is an only child. She has a good relationship with her mother with whom she shares intimate thoughts and feelings and a positive, companionate relationship with her father with whom she shares enjoyable activities. Neither parent is prepared to affirm her, although they have told her that she is loved and wanted. She has been formally diagnosed on the Autism Spectrum, Level 2. Alicia has experienced school refusal, suicidal ideation, depression, peer relationship difficulties, and identity confusion. At the time of writing, Alicia had been in therapy once a week for 18 months. During this time, she had returned to school, recovered from her depression, ceased her suicidal ideation, and started to think about her future.

Developmental history

Alicia's parents had no concerns about her gender development in early childhood. There was one occasion when Alicia was 7 or 8 when told her mother that she wanted to be a boy. She had early puberty at age 10 in grade 4 and this was very unsettling for Alicia, who expressed discomfort with her developing breasts and hips. She wanted to cover up more and changed her clothing preferences.

Alicia was bullied and excluded from peer groups. She moved in and out of peer groups but was frozen out by bullies. She befriended different girls but found out that they did not regard her as a friend – they just allowed her to "hang out" with them. She was "broken hearted".

Alicia was diagnosed ASD in grade 6. Alicia wanted to get her long hair cut off. She started wearing boys' clothes. She was unhappy with her female genitalia. She started questioning her gender and became hyper focused on the internet – into YouTube, Discord, etc. She told her mother she didn't understand why everyone didn't question their gender. Mother closed off access to Reddit and Tumblr.

At the time of referral, Alicia had an online boyfriend (15) who is gay. She has not admitted to him that she is a girl. She thinks she is in a gay relationship. Mother thinks that she has told him that she is intersex and has male genitalia and that she is trans. Her mood improved once this relationship began. They play Minecraft online together, chat about life. Alicia feels guilty about lying to him about her gender.

In year 7 (the first year of high school) a male student liked her, but she didn't pick up the cues. Another boy tried to get someone to have sex with her. He cornered her in the bushes and invited other boys to "fuck" her. It all got reported to school management, boy was suspended, but Alicia she was severely traumatised. She became suicidal and could not get the incident out of her mind, could not go to that space in the school grounds. One day, she climbed the stairs in a school building with the intention of jumping off, but boy(friend) came and distracted her to go to the library. The school got someone to accompany her to classes to keep her safe. She started to school refuse.

Mother said that suicide became Alicia's "go to" to solve her problems, but she is not unduly concerned about her safety. Her main concern is the GD. Mother sees her as her daughter, cannot use the alternative name or pronouns.

Mother thinks her husband is also on the autism spectrum. He loves Alicia but cannot talk comfortably with her. She rarely goes to him with problems.

First month of therapy

Session 1

> I have spent three years trying to figure out my gender identity and why I have gender dysphoria (GD). This year, I have found out and feel comfortable. I have told my parents, but they are not taking me seriously. They have barred me from doing stuff that might help me – they don't understand how I feel about my gender. My friends use my preferred name and pronouns (he/him), but my parents refuse.
>
> My relationship with my parents is good except for the gender issues. We are strained over that – I feel isolated around them. I feel I can't go to them. They give me reasons as to why I shouldn't be trans. I am being encouraged not to explore how I feel because

of what my Mum has read. I want to tell them that I feel mistreated by them for not respecting my chosen name and pronouns.

Most of my classmates are not accepting either; they make jokes about trans people, so I am hesitant about using my chosen name and pronouns at school.

I have online friends I feel close to. Two of them know that I am trans and are accepting. Others don't know but I go by my trans name and pronouns online because it relieves my distress. They are struggling with stuff as well.

I started wondering about my gender when I was 10 which is when I started puberty. I felt something was "off" about myself. I tried to understand it by experimenting with different identities and what felt right for me. I explored them all, but nothing felt right, I couldn't stick to one thing. I was all over the place. I knew about trans people while I was trying to figure myself out. At the beginning of 2020, I finally found an identity that I was looking for but then had trouble expressing that and finding acceptance. At one point, I considered myself non-binary (NB), gender fluid (GF), agender. I landed on non-binary because I don't identify as male or female; GF fluctuates between the poles of male and female. But NB didn't feel right either, thinking of myself as other than male or female. GF felt like something that I had to actively think about all the time. "What do I feel like right now – male or female?" Then I decided that trans felt best for me – it felt like I could recognize who I am – I really wasn't comfortable with being female. Saying that I am trans feels right in the sense that I now know who I am.

As a female, I experienced GD, didn't like my female pronouns, within my peer group at school, I felt very disconnected from girls in my classes, slowly gravitated towards having a male peer group, with whom I felt more comfortable. They don't acknowledge my trans status except when they are making jokes about trans people. At school, I still go by my birth name and female pronouns. My male peer group see me as the only girl in their friend group. One of them reads me as more masculine, sometimes uses male pronouns then corrects himself. Secretly, I don't want him to correct himself but none of them know that I am trans.

Some students in class make awful jokes about trans people, making fun of NB people. In a science class we had to classify salts and gases. Some of them related this to trans categories. I had to sit there pretending that I didn't care about what they were saying. I was on the verge of breaking down, so I left to go to the bathroom. I was crying for the last ten minutes of period in bathroom. They were jabs at me personally. They figured I was part of the LGBTQ community.

Second month of therapy

The only thing that I want at the moment is to transition socially without going through more struggles and to feel more comfortable with myself. I also want to get a binder to feel more comfortable. Mum says no - she says she wants me to be comfortable in my own skin but I can't without doing anything. I wear sports bras and baggy clothing, but sports bras don't help much. My height is a problem because I am short, I am insecure with that. I also have bottom dysphoria – I am distressed at not having a penis. I have to wear loose pants to stop myself from being more aware of it. Having a penis would make me feel more comfortable and more complete.

I am attracted to guys. I have a boyfriend. He knows that I am trans and he genders me correctly. My parents know that I have a boyfriend. He is 15, a year older than me.

I feel vulnerable and distressed at home and school. I would like my parents to be more accepting so that I can come to them with the issues that I am having. I would like to socially transition just in the house, I would feel more comfortable, just around my parents. There wouldn't be too much change. I have a lot of body hair - Mum says that I should shave my legs and armpits, but I prefer not to.

Six months into therapy

I have had some moments doubting my gender identity, sometimes I feel confused that I am faking it and doing it for attention. It comes and goes. It's quite distressing, I want to tell Mum and Dad that I am having doubts and need some comforting words. It is hard to let them know that I am not trans anymore because when I am doubting it is very hard to stay grounded. It feels like a big swamping feeling that I am overwhelmed by, and it is hard to reach out for comfort to them. I am scared that they might take my doubting as a good thing. Mum is OK with other stuff but not for my

gender dysphoria; we are at opposite ends. We can't see eye to eye. There is a lack of understanding about how I am feeling. I talked to her before about my breast dysphoria. I said to her, "I don't like my breasts." My mother then said, "Well, I don't like having fat legs."

Conversation with mother:

What is worthy of note is that Alicia started taking her bra off to sleep while we were on holidays at the beginning of December, and she has kept doing that. She had refused to do that for about a year. Also, she would always hide her breasts with her arms when in the bathroom, going to the bathroom without clothes on, or whatever, but is no longer doing that since sleeping without the bra. She even unzipped her sun shirt while in the pool, which has not happened for a few years. She had swimmers underneath, but normally would never expose herself that much. Four or five days ago, she was upset, but didn't tell me until after, but said it was to do with gender dysphoria and doubting herself. I didn't want to push her, but I took that to mean she doubted she was trans, and that's what was upsetting her - the thought of not being trans.

12 months into therapy

My thinking has changed about the gender issues over time - I feel once again that I am not sure who I am regarding gender. I want to block out everyone else's opinion because it is a life changing issue. Questioning has the potential to be life changing. I am at a point where I feel I have to go through it alone, to avoid multiple opinions. There is no check list that definitively says what you are. I have to step back from everyone and dive deep down into myself to try to know who I am. It is a very tricky experience to try to explain. I feel like I know how I stand, how I perceive myself in terms of gender but there is no way I can know for sure. I might feel one way now and will be treated in a certain way but then I might change my mind.

Alicia's current summation, 18 months into therapy

I have decided that I am a nonbinary male, but I am not necessarily male. My gender is neutral – overall, I am in the middle of thinking about it on a spectrum. I feel that I have now landed on something that feels right; it is the best descriptor for me. I

> previously considered myself trans FtM but now that doesn't fit. I have made peace with it. I have made peace with the fact that I have been born with a female body. I might not like it, but it is my body and the best I can do is try to feel at home one way or the other in it. When I think about medical transition - I will leave that alone until I am 18 and responsible for my own choices. Hopefully, I would have a firm grasp on who I am by then. Medical treatment is risky for people who are going through puberty, and I am too old now to have puberty blockers, so I have decided to get to the end of this, I mean puberty, being a teenager. I don't want to make irresponsible decisions when I am not mature enough to do so. I think I will eventually start testosterone, but not too rapidly. I want more masculine features/characteristics, but I prefer to appear androgynous, more male leaning androgyny. I want to minimize my overtly feminine features that get to me. I expect to shave but not have a bushy beard, maybe minimal hair on my face. I have never grown any facial hair. I don't like having wide hips or a curvy body. I want bulkier arms and bigger hands. My body is "petite" - I don't like that. I am short and insecure about my height. I am 157 cms - that is short compared to my classmates. I am embarrassed that I am so short compared with my classmates. I feel inferior having to look up to them. In my friend group, I am the oldest but also the shortest. I want more respect.

I asked Alicia whether she will get more respect if she looks more androgynous. She replied:

> It is a grey area for me. In terms of feeling respected, I want to feel like myself, like a proper person. Sometimes I am shambling around as some thing and not as any sort of defined me. I really don't like the fact that I have a fanny. I am tolerating the breasts more than the fanny. Having a fanny doesn't feel right or proper. It feels like empty space. It doesn't feel like a part of my body. My ideal body would not include a fanny. I would rather have a willy.

I explained how testosterone would and would not change her body. I told her that it would produce facial hair and a deeper voice but would not increase her height or grow a penis. She was somewhat shocked to hear about these limits of testosterone. She then said, “In that case, I will leave the big decisions until I am 18”.

These statements from this young ASD person highlight how young people's sense of gender changes over time and how dangerous it is for gender clinics to accept their first pronouncements of how they perceive themselves. It also brings into sharp focus the misunderstandings and confusion that can arise. Without careful discussion in a safe space, such misconceptions may never be detected or corrected, and the young person may be left with their erroneous beliefs, the basis upon which they make irreversible decisions about their bodies. It is also noteworthy that a significant proportion (~51%) of young people with ASD express anxiety related to gender while not expressing unhappiness with their biological sex (60%) or a desire to change their biological sex (70%)[30]. It is therefore imperative that anxiety about gender not be used as the determinant for medical interventions in ASD populations.

Jared[31]

Below is a two-year history summarizing the gender identity and sexual orientation trajectory of an adolescent male. Apart from his gender questioning, Jared was an otherwise psychologically healthy young person from an intact family. He loved BMX and scouts, was doing well at school, had friends, both male and female, and two older siblings, including a 23-year-old brother who proved a very useful ally and role model in Jared's treatment.

At the age of 14, Jared came out to his parents as GAY. He soon changed that declaration to BISEXUAL when he experienced a powerful crush on a female classmate. After she rejected him, he came out as TRANS and demanded puberty blockade and cross sex hormones.

In therapy, his demands for transition were strident and incessant. He constantly asked me when I was going to tell his parents that he was competent to give consent and could therefore proceed with his transition.

He shaved his legs, arms, and body hair, grew his hair long, and started to wear eye makeup and nail polish. He ordered female clothing from the internet and wore it secretly in his room. When his parents confiscated these clothing items, his female friends from school lent him

[30] Adesman, A., Brunissen, L., & Kiely, B. (2020). Characterization of Gender-Diverse Expressions and Identities among Youth with Autism Spectrum Disorders. *Pediatrics*, *146*(1_MeetingAbstract), 302-303.
[31] A very similar case has been posted online https://genderclinicnews.substack.com/p/florida-warns-doctors-off-gender?r=130uly&s=w&utm_campaign=post&utm_medium=web

their clothes to wear until I advised his parents to put a stop to this. Teachers at his school started calling him by his preferred name and pronouns until I advised his parents not to allow this.

He became increasingly hostile towards me because I was not advising his parents to allow him to transition. His parents had told him that they were not prepared to act on his desire to transition until they were advised by me that this was the medically and psychologically sound course of action. I told Jared that such decisions required great care and exploration and that we needed to understand more about his motivation for wanting to transition and what it meant in his life. I explained that I needed to be sure that he understood all the ramifications of such treatment and the fact that some aspects were irreversible. He insisted like so many young transgender declaring adolescents that he didn't care about having sex or children so none of that mattered.

Several months after therapy commenced, while still vehemently protesting his trans-female identity, he wrote a letter to his parents apologising for misleading them. He said he now realised that he was not a trans-female but a DEMIGIRL (denoting partial non-binary, partial female gender identity).

He changed this orientation shortly thereafter to DEMIBOY (denoting partial non-binary, partial male gender identity). He stopped trying to deceive his parents with regards to wearing makeup and nail polish and secretly stashed his female clothing obtained illicitly through the internet (with packages delivered to his friends' houses so that his parents did not suspect) into the recycle bin.

Three months later, he again wrote to his parents, telling them that he was only joking about the whole thing and that they were the only people who had taken it seriously.

I advised his parents to eat humble pie to give their son the opportunity to exit the gender maze without losing face.

The next day, shortly after his 16th birthday, he asked his parents to take him for a haircut and to take him shopping for new clothes. He directed them to a barber and a male clothing store. He quietly advised his parents that he now realised that was STRAIGHT.

SOCIALIZED AND INTERNALIZED HOMOPHOBIA

An adolescent realises that s/he is same sex attracted. Finding this unacceptable, due to parental and/or internalized homophobia, the adolescent reasons as follows: Being same sex attracted is bad and shameful. My parents will reject me if I am gay. If I am a boy attracted to other boys, I must be a girl and therefore need to transition so that my attraction to boys becomes heterosexual.

Hossein

Sociocultural issues and parental homophobia

Hossein was aged 15 years when his parents contacted me about their many concerns for their son. He is the elder of two children; he has a nine-year-old sister. The family migrated to Australia from a Balkan country when Hossein was five. They became panicked when Hossein declared that he was transgender and wished to transition immediately.

Hossein was difficult to engage except when talking about his gender dysphoria and pressing his case for transition. He said that his parents were waiting for my assessment before they agreed to any medical treatment. He asked several times each session when I would finish my assessment and advise his parents that he could start taking oestrogen. He was otherwise hard to engage and was sometimes irritated, sleepy, and uncooperative.

Hossein expressed concern about his schoolwork. He had aspirations to study aerospace engineering but was finding senior school maths and physics difficult. He also reported serious attentional problems. I advised his parents to obtain psychometric assessments of his ability, attention, and social skills in order to gain a baseline of his current functioning. Hossein was found to have average intelligence, which was not concordant with his parents' view of him, or his own view, that he was "gifted." I attempted to do some reality testing regarding parental expectations for his academic performance.

Hossein also scored in the clinical range for both attention deficit disorder and autism spectrum disorder. I indicated to his parents that these conditions were priorities for treatment and that the school needed to be informed about the results of psychometric testing in order to better support Hossein at school.

When I explored Hossein's perception of his sexuality and sexual orientation, Hossein disclosed the following:

> I see myself as bisexual. I have feelings for guys and girls, more like a pan-thing. I have had a boyfriend who identifies as male and pan since last year. We get together just the two of us - we visit each other's houses. I guess I would be OK with being gay. For me, it fluctuates.

Of his mother, Hossein said:

> Mum knows I have this friend. She doesn't know that he is my boyfriend. I don't think Mum will take it well because she asked me if I still liked girls. She wouldn't take kindly to knowing I have a boyfriend.

Of his father, Hossein said:

> Dad is trying to suppress his queer phobia, but he says bad things about LGBTQ. He is anti it all; he got angry with me for refuting what he was saying. Dad said gay is about anal sex and that is gross. Then Mum told him to shut up and I went to my room and cried. Dad is anti queer for sure, he tries to suppress it because he still loves me. I felt very disappointed in Dad when he expressed these sentiments. He will be very freaked out if he thinks I am queer, gay, or trans.

This is a [….] family who speak [….] at home. [….] culture is homophobic. In a family meeting, I tentatively prepared his parents for the possibility that Hossein's sexuality may eventually resolve as homosexual and that if that were the case, they would need to resolve their own antipathy to homosexuality in order to support their son.

Declaring oneself transgender in this sociocultural milieu is an attempt to resolve the difficult dilemma of a […] boy being gay. Sadly, transgender identity is preferred to a homosexual orientation in certain Balkan countries and the Middle East.

Hossein was insistent at various times that he was transgender and was impatient to commence his social transition and to obtain prescriptions for cross sex hormones. He was dismissive of the life changing effects of these drugs on his body, was indifferent to the loss of sexual function, and declared that he was not interested in preserving his sperm for later reproduction because he had no intention of having children. Hossein was cognitively rigid

and evinced concrete thinking when discussing his potential transition. He had researched the "facts" about MtF transition but could not discuss them in a nuanced way or accept the possibility that he may be disturbed by side effects or uncertainties about his course of action. He did not wish to proceed with surgery at this time.

In view of Hossein's recently diagnosed ADD, ASD, and uncertainty about his gender identity and sexual orientation, I drew the conclusion that Hossein was not Gillick competent and should not be supported to transition at this time, either socially (i.e., changing his name and pronouns) or through cross sex hormones.

The priority for Hossein was to address his ADD and to get support for his ASD. I referred him to a child and adolescent psychiatrist for a medication review for his ADD and depression. The psychiatrist prescribed methylphenidate and antidepressants. I ceased therapy with Hossein as he refused to engage further because I had not supported his transition and had several further sessions with his parents to assist them to address their homophobia and grief that their only son was, in all likelihood, gay.

Roisin

Internalised homophobia

Roisin is a 15-year-old adolescent attending an exclusive girls' school. She came out as trans to her mother at the age of 14. It seemed like rather a half-hearted coming out. Roisin had not chosen a new name or pronouns and did not seem particularly interested in exploring her new identity. The only change was that she asked her mother to buy her the alternative school uniform, which consisted of trousers and a shirt instead of a pinafore. This did not trouble mother too much as a significant number of the students had opted for this style of uniform.

Roisin's presentation was more consistent with body dysmorphia than gender dysphoria. Roisin complained that her hips were too wide, that her thighs were too big and that her face was the wrong shape although she could not be specific about what it was about her normal, symmetrically placed features that were so wrong. Roisin suffered from severe acne for which she was prescribed medication. When her skin cleared up and she appeared in the full bloom of good health, she confided to me that she was not that happy that her skin looked so good. When I inquired why, she replied that now that the focus was taken away from her acne, all

the other "hideous" features of her countenance were in the full glare of the spotlight, and she could not tolerate looking at herself in the mirror or having her photo taken.

Roisin is gifted and had been performing well at school, but teachers had commented recently that she was distracted, disconnected, often "spaced out" and not "with it" in class. She appeared sleepy and often put her head on the desk. In response to a question about how she was sleeping, Roisin responded:

> I am having nightmares about events in my life and about what could go wrong. They are most often about peer interactions. I worry about potential issues related to my peers judging me, exposing me as gay. I wake up in a panic about who is talking about me. There are a few girls in my class who won't shut up about LGBTQ issues. They are really obnoxious and loud, and I always feel as if they are referring to me when they talk about lesbians in a disparaging way. I have thought about asking them not to keep talking about LGBTQ issues all the time, but if I do that, I will be accused of being homophobic. I might risk being ostracized by other girls as well.

Soon after she reported her nightmares, Roisin disclosed that she had been self-harming for about a year.

> Sometimes, I come home from school defeated, nothing in particular has necessarily happened, it is just the constant stress of the environment. I tried sitting with the feeling, but it didn't pass, so I got the reed on my clarinet and scraped and cut my waist and hip. It is still red and angry, it was painful, but it is healing. Other times I use scissors and cut the top of my thighs. I only cut where it is not obvious, and no-one will see it.

About nine months into therapy, Roisin confided that she had a powerful crush on a girl at school but would never act on it for fear of rejection by the girl in question, and peer vilification in general. She was very troubled by the intensity of her feelings and asked me whether she was gay.

I had a very open and scientifically oriented discussion with Roisin about female sexual orientation. I explained that sexual orientation in females appears more likely to change over time. I discussed hypotheses regarding the greater sexual orientation fluidity in females

compared with males that are underscored by biologically based sex differences in foetal hormone exposure and socio-political forces that constrain sexual self-concept, expression, and opportunities differently in women and men. I indicated that while she currently felt strongly same sex attracted, her feelings may well change over time. I explained that many adolescents experienced same sex attractions but mostly reached adulthood as heterosexual. I normalized her feelings and explained that she was not inferior, diseased, or immoral if she were, in fact, gay. Roisin was greatly relieved by our several discussions on female sexual orientation and decided that she would like to share this with her mother.

I coached mother about appropriate responding and reinforced what I had already discussed with Roisin in her sessions. Mother was relieved that Roisin no longer thought of herself as trans and was not at all troubled that she may be lesbian. She said:

> Being gay is biologically based and does not involve self-mutilation or lifelong patienthood at the behest of the medical profession. There are a number of gay people in our extended family, and all are accepted without question. We do not have a problem with it at all.

The disclosure went well, and Roisin was greatly comforted by her parents' easy acceptance of her declaration. However, she is troubled by possible responses from her peer group should they find out (she has no intention of disclosing to them). She continues to struggle with other aspects of her mental health, including a treatment resistant clinical depression for which she has been medicated unsuccessfully.

Professor Dianna Theadora KENNY Mob: [redacted]
E: [redacted]
ABN [redacted]

Professor of Psychology (rtd)
Consultant Psychologist and Psychotherapist

Registered psychologist (No. 0005390)
AHPRA number PSY0001136350, specialist endorsements: developmental, educational and counselling psychology
Medicare Provider No 2876971T

Marriage and Family Therapist (Relationships Australia)

Nationally Accredited Mediator (Australian Dispute Resolution Association)

Family Dispute Resolution Practitioner (No. R1005291) (NSW College of Law)

ABBREVIATED CURRICULUM VITAE

Current	2019 -	Principal, DK Consulting (Psychology, psychotherapy, family dispute resolution, and medico-legal services)
Previous appointments	2013-2019	Hon Professor of Psychology, The University of Sydney
	2006-2013	Professor of Psychology, The University of Sydney
	1988-2006	A/Professor, Senior Lecturer, Lecturer in Psychology, The University of Sydney
	1986-1987	Psychologist in private practice
	1986-1987	Lecturer in School Counselling, School of Counselling and Disabilities Studies, The University of Western Sydney
	1983-1985	Regional Specialist Counsellor for Emotionally Disturbed Children, Liverpool region, Division of Guidance and Special Education, NSW Department of Education
	1978-1983	District School Counsellor, NSW Department of Education
	1976-77	Teacher, Haberfield Demonstration School, Haberfield, NSW

University Qualifications

1988	Doctor of Philosophy (PhD) (Developmental and Educational Psychology), Macquarie University (School of Behavioural Sciences)
1980	Master of Arts (School Counselling), [M.A. (Sch. Couns.)], Macquarie University (School of Behavioural Sciences)
1974	Bachelor of Arts (Honours - Psychology) [B.A. (Hons)] The University of Sydney

Other Qualifications

2016	Postgraduate Diploma in Family Dispute Resolution (PG Dip FDR) (NSW College of Law)
2015	Nationally accredited mediation training – Resolution Institute
1986	Diploma in Clinical Hypnotherapy (DCH), Australian Society of Clinical Hypnotherapists

1982	Certificate in Marriage and Family Therapy, Marriage Guidance Council, N.S.W. (now Relationships Australia).
1977	Associate Diploma in piano, Trinity College of Music, London (ATCL)
1975	Diploma in Education, (DipEd) Sydney Teachers' College

Registrations and Accreditations

Psychology Board of Australia (No.0005390)

Australian Health Practitioner Regulation Agency (PSY0001136350)

Approved Medicare provider (No 2876971T)

Nationally accredited Mediator (LEADR, Australian Dispute Centre)

Family Dispute Resolution Practitioner (NSW College of Law)(Registered with Attorney General Department) (No. R1005291)

Membership of professional societies

Member, Australian Psychological Society: Specialist Accreditations

Academic Member, College of Developmental and Educational Psychologists

Fellow, APS College of Counselling Psychologists

Member, American Psychological Society

Member, Society for Psychotherapy Research

Member, International Association of Relational Psychoanalytic Psychotherapy

Elected Member, New York Academy of Sciences

Member, Australian Dispute Resolution Association

International affiliate, American Psychological Association

Consultancies relevant to psychology and the law, transgender issues in children and adolescents (informed consent, assessment and suitability, family conflict, comorbid conditions), child sexual abuse, sex offending, and sexual misconduct

Expert report writer, Human Rights Law Alliance

Expert report writer, Amicus Briefs for cases occurring in Canada and USA

Expert reviewer/report writer, Office of the Director of Public Prosecutions, Armidale, Gosford, Lismore, Parramatta, Penrith, Sydney, Tamworth, Wollongong

Expert reviewer /report writer, Crown Solicitors' Office, Sydney

Expert reviewer/report writer, Victorian Government Solicitor's Office (VGSO)

Expert reviewer/report writer, Joint Investigative Response Team (JIRT), NSW Police – Blacktown, Chatswood, Coffs Harbour, Manly, Penrith, Tamworth

Expert reviewer/report writer, Health Care Complaints Commission (HCCC) – NSW, Victoria, and Western Australia

Expert developmental psychologist, various Barristers chambers

Assessment psychologist, Aboriginal Legal Service

Research consultant, *NSW Department of Juvenile Justice*

Research consultant, *Justice Health NSW*

Research consultant, *Youth Justice Coalition* (pro bono)

Research consultant, *Public Interest Advocacy Centre* (pro bono)

Consultant investigative psychologist (of alleged child sexual abuse), *St Joseph's College, Hunter's Hill*

Consultant psychologist, *Tribunal of the Catholic Church*

Expert reviewer for Joint Investigative Response Team, NSW Police

- Provide advice and court reports on cases related to child sexual assault, including reports of historical child sexual abuse
- Appraise the quality and plausibility of disclosures made by complainants in cases of current and historical sexual abuse
- Provide literature reviews and advice on the status of recovered memories, the reliability of childhood memory, and memory processes over time and factors that can alter or affect memories
- Provide advice on language development, children's use of and understanding of sexual language
- Provide expert advice on other matters related to criminal offending against children.
- Provide expert advice on the nature of psychopathologies arising from child sexual abuse

Expert developmental psychologist for various Barristers chambers, Crown Solicitor, and Office of the Director of Public Prosecutions

- Provision of expert reports on matters pertaining to child development
    - credibility and reliability assessments of disclosures of child sexual abuse
    - Reasons for delay of disclosures of child sexual abuse
    - memory and language development as it pertains to child sexual abuse disclosures
    - evaluation of "recovered memories"
    - Long term impacts of child sexual abuse
    - Capacity for consent

Court referred clients

- In cases of parental alienation, assess the quality and veracity of accusations of emotional, physical and sexual abuse of children in divorcing couples undergoing family court proceedings for custody and access of the children of the marriage, and report these findings to the court.
- Assess parenting capacity in separating and divorcing parents to ascertain child safety and capacity of parents to undertake shared parental responsibility.
- Where mandated by the court, provide assessment, counselling and therapy for accused fathers and report on the alleged risks to their children while in their care.

Expert reviewer for the Health Care Complaints Commission

- Investigate complaints against psychologists for malpractice and misconduct, including sexual misconduct, and other conduct that falls below the standard expected of the profession.
- Undertake review and critical appraisal of treatments offered by psychologists and whether those treatments have been collusive, coached, suggestive or in other ways biased with respect to issues of child sexual abuse, including historical sexual abuse.

- Evaluate psychologists' psychological practice, evidence-base for therapeutic interventions, and competence in implementing psychological therapies.

- Undertake file review of documents (letters, submissions, complaints, statements, accounts of therapy, therapy case notes) from complainants and defendants, report writing, participation in conclaves, and court appearances.

Consultant Psychologist to the Tribunal of the Catholic Church

- Assessment of marriages for annulment
- Assessment of claims of sexual abuse within marriage and non-consummation of marriage, among other relationship issues.

Research on sexual offending in young sex offenders

- Extensive research undertaken on sexual offending examining life histories and precursors to sexual offending, young offenders' experience of sexual abuse, and other forms of maltreatment for the NSW Department of Juvenile Justice.

Ministerial and other Appointments in Psychology and the Law

2013 Board Member, Daystar Foundation (a foundation for the provision of vocational training and employment to 'at risk' young people)

2003-2009 Chair, Ministerial Steering Committee, NSW Department of Juvenile Justice Collaborative Research Unit

2003-2009 Member, Ministerial Steering Committee on Sexual Offending, New South Wales Department of Corrective Services

2002 A/Chair, Ministerial Reference Group on Sexual Offending, New South Wales Department of Corrective Services

2001 Member, Ministerial Reference Group on Sexual Offending, New South Wales Department of Corrective Services

2003 COCQOG (Commonwealth Cost and Quality of Government): External Reviewer of Psychological Services and Specialist Programs, NSW Department of Juvenile Justice

1996-2002 Deputy Chair, Ministerial Steering Committee, NSW Department of Juvenile Justice Collaborative Research Unit

1997-2003 Chair, Research and Ethics Subcommittee, NSW Department of Juvenile Justice Collaborative Research Unit

Expertise

I divide my expertise into five key areas –

(a) Gender dysphoria (GD) in children and adolescents including a clinical practice working with young people with GD and their parents/families and schools. I bring my decades of experience working with children and families to my practice in working with young people with GD (key areas b, c, d, and e are all relevant to my clinical practice in gender dysphoria).

(b) Child development – including children's social, emotional and cognitive development, assessment of children's attachment to primary care givers, peer relationships, cognitive abilities including intelligence, memory and language; assessment of developmental psychopathologies and behavioural disorders and provision of therapy for same.

(c) Matters pertaining to child sexual abuse, including the disclosure of child sexual abuse, the impact of sexual abuse on children, historical child sexual abuse and its reporting, and issues of repressed or false memory, grooming by paedophiles, and counter-intuitive behaviour.

(d) Matters pertaining to school performance and achievement, psychometric assessment of intelligence, assessment in literacy and numeracy and specific learning disabilities.

(e) Family dispute resolution (I am an FDRP registered with the Attorney General's Department) in which role I asses alleged offences of one parent against another and/or their children in the context of family court proceedings. I report on issues such as access, parental alienation, and child stress in the context of contested divorce and custody disputes.

(a) Gender dysphoria in children and adolescents

I have a busy clinical practice specializing in the treatment of gender dysphoric children and young people, their parents and families. I have contributed invited submissions to government here in Australia and overseas on matters relevant to education policy on transgender declaring children and adolescents and acceptable therapies with which to treat them. I have published in the area and provided expert reports on disputes regarding treatment of gender dysphoric young people whose cases reach the Family Court.

Key publications (Books, edited books, book chapters, journal articles)

Kenny, D.T. (2020). *Gender dysphoria in children and young people: Collected papers on the psychology, sociology and ethics of gender transitioning*. Germany: Scholars Press.

This book critiques gender dysphoria in young people and its current treatments that include gender affirmation therapy involving puberty blocking agents, cross sex hormones and sex reassignment surgery. I examine the safety of these treatments, evidence of efficacy, capacity of children and young people to give consent to life altering treatments, the social impacts of transgender individuals, particularly in women's sport, and the social contagion of gender dysphoria.

D'Angelo, R., Syrulnik, E., Ayad, S., Marchiano, L., **Kenny, D. T.,** & Clarke, P. (2021). One size does not fit all: In support of psychotherapy for gender dysphoria. *Archives of Sexual Behavior*, *50*(1), 7-16.

Holloway, G., **Kenny, D.T.,** Deves, K., …Parkinson, P., Morris, P., & Halasz, G. (2021). Australian perspectives on transgendering children and adolescents: Implications for policy and practice. Hobart: Author.

Kenny, D.T. (2021). *Opposing the teaching of gender fluidity ideology: The Education Legislation Amendment (Parental Rights) Bill 2020* (pp. 13-22). In Holloway, G., **Kenny, D.T.,** Deves, K., …Parkinson, P., Morris, P., & Halasz, G. (2021). Australian perspectives on transgendering children and adolescents: Implications for policy and practice. Hobart: Author.

Kenny, D.T. (2021). *The social contagion of gender dysphoria: a theoretical and empirical proposition* (pp. 56-70). In Holloway, G., **Kenny, D.T.,** Deves, K., …Parkinson, P., Morris, P., & Halasz, G. (2021). Australian perspectives on transgendering children and adolescents: Implications for policy and practice. Hobart: Author.

Submissions to government inquiries

Kenny, D.T. (2021). Submission to the NSW Parliamentary Inquiry: Education Legislation Amendment (Parental Rights) Bill 2020.

https://www.parliament.nsw.gov.au/lcdocs/submissions/70648/0005%20Professor%20Diana%20Kenny.pdf and

https://www.parliament.nsw.gov.au/lcdocs/inquiries/2610/Report%20No%2044%20-%20PC%203%20-%20Education%20Legislation%20Amendment%20(Parental%20Rights)%20Bill%202020.pdf

Kenny, D.T. (2020). Gender development and the transgendering of children. In H. Brunskell-Evans and M. Moore. *The fabrication of the transgender child*. Cambridge: Cambridge Scholars Press.

Kenny, D.T. (2020). Submission and invited presentation to the Queensland government Inquiry into the proposed *Health Legislation Amendment Bill 2019* to outlaw conversion therapy.
https://diannakenny.com.au/images/pdfs/Submission_to_the_Queensland_Inquiry_into_Outlawing_Conversion_Therapy.pdf and
https://documents.parliament.qld.gov.au/tableOffice/TabledPapers/2020/5620T328.pdf

Kenny, D.T. (July 2020). Submission to the ACT government into proposed amendments to outlaw conversion therapy.

Clinical guidelines

Morris, P. …. **Kenny, D.T**….. (May, 2021). *Managing Gender Dysphoria/Incongruence in Young People: A Guide for Health Practitioners.* National Association of Practising Psychiatrists. https://napp.org.au/2021/05/managing-gender-dysphoria-incongruence-in-young-people-a-guide-for-health-practitioners/

Presentations

Kenny, D.T. (2021). *Transgendering our young people: Faulty science, psychic epidemic.* Invited lecture to the Faculty of Medicine, Notre Dame University, Sydney, Australia.

Kenny, D.T. (2020). *Affirmation only: Where's the evidence.* Invited presentation to the Catholic Medical and Bioethical Conference, 30 May.

Kenny, D.T. (2020). *Is gender dysphoria socially contagious?* Invited presentation to the NSW Parliament Forum on gender dysphoria in our young people, 18 February.

Kenny, D.T. (2020). *Transgender "ideology" and the "trans-gendering" of young people.* Invited presentation to the Northern Area Mental Health Network, NSW Department of Health, 12 February.

Kenny, D.T. (2019). *Children and young people seeking and obtaining treatment for gender dysphoria in Australia: Trends by state over time (2014-2018).* Paper presented at the Forum on transgender children and adolescents at the Parliament of NSW, 2 July, 2019.

Children and young people seeking and obtaining treatment for gender dysphoria in Australia: Trends by state over time (2014-2018) - Professor Dianna Kenny

Kenny, D.T. (2019). Female sport participation and gender affirmation: A collision course for medical ethics. Invited presentation Melbourne consortium of parents of transgender declaring children. 12-13 October.

Female sport participation and gender affirmation: A collision course for medical ethics - Professor Dianna Kenny

For other significant contributions to the gender dysphoria debate, go to https://www.diannakenny.com.au/

(b) Child and adolescent development

(i) I commenced my professional life as a primary school teacher, then became a school counsellor, and specialist counsellor for emotionally disturbed children with the NSW Department of Education. I held these positions for 10 years before joining The University of Sydney, where I rose to the rank of Professor of Psychology in 2006.

(ii) I hold a PhD in developmental and educational psychology, a master's degree in School Counselling, an honours degree in psychology and postgraduate diplomas in education and family dispute resolution.

(iii) I am a recognised expert in child development. I have designed and lectured in a range of courses at undergraduate and postgraduate levels pertaining to child development including: Developmental psychology; developmental psychopathology; infant and child study (with a focus on language and cognitive development); attachment theory; the psychological and cognitive assessment of children; and the developmental foundations of stress and coping.

(iv) I have major publications in the area of child development.

(v) I have provided reports on children to the courts and police, including on issues in child development such as language and cognitive development, childhood memory and its reliability, and adverse experiences that impair normal development such as attachment trauma and environmental risks to safety and security.

(vi) I am able to provide comprehensive literature reviews on most subjects related to child development.

Key publications:

Kenny, D.T. (2013). *Bringing up baby: The psychoanalytic infant comes of age.* London: Karnac.

This book examines the development of children, from birth to adolescence. It provides a detailed analysis of all modes of development including cognitive and social development, language development, the development of memory, the role of secure attachments in emotional development and the contribution of developmental neuroscience to our understanding of infant and child development.

Kenny, D.T. (2007). *Lifespan development: Theories and research.* The University of Sydney: Author.

This comprehensive manual describes how people develop and change throughout the lifespan, critically evaluates how cultural, historical, and economic factors influence development, presents the major psychosocial, emotional, and cognitive developmental theories, discusses the major controversies in developmental psychology, integrates different theoretical perspectives on development, and applies developmental theory to healthcare practice. It includes a critical review of the methods and research approaches (including genetic, comparative, cross cultural, ethological, and ecological) in developmental psychology and research designs (including cross-sectional, cohort and longitudinal, time lag and sequential).

Schofield, P., Mason, R., Nelson, P.K., **Kenny, D. T.,** & Butler, T. (2018). Traumatic brain injury is highly associated with self-reported childhood trauma within a juvenile offender cohort. *Brain Injury,* DOI: 10.1080/02699052.2018.1552020.

Kenny, D.T. (2016). The adolescent brain: Implications for assessing young offenders' legal competence. *Judicial Officers' Bulletin* (Judicial Commission of NSW), April, 28, 3, 23-27.

Kenny, D.T., Blacker, S. & Allerton, M. (2014). *Reculer pour mieux sauter*: A review of attachment and other developmental processes inherent in identified risk factors for juvenile delinquency and juvenile offending. *LAWS,* 3, 439–468; doi:10.3390/laws3030439.

Kenny, D.T., & Nelson, P.K. (2008). *Young offenders on community orders: Health, welfare, and criminogenic needs*. Sydney, Australia: Sydney University Press. ISBN 978-0-9804117-0-6.

Kenny, D.T. (2001). Cognitive-developmental theory. In Carol Jones (Ed). *Readers' Guide to the Social Sciences Volume 1, pp. 230-231.* London, United Kingdom: Fitzroy Dearborn Publishers.

Kenny, D.T. (2001). Nature and nurture. In Carol Jones (Ed). *Readers' Guide to the Social Sciences Volume 1, pp 1105-1106.* London, United Kingdom: Fitzroy Dearborn Publishers.

Kenny, D.T. (2000). Psychological foundations of stress and coping: A developmental perspective. In Kenny, D.T., Carlson, J. G. McGuigan, F. J. & Sheppard J. L. (Eds.). *Stress and health: Research and clinical applications*. Ryde, NSW: Gordon Breach Science/Harwood Academic Publishers (pp. 73-104).

Kenny, D.T. & Waters, B. (1995). Current issues in adolescent mental health. In D.T. Kenny and R.F.S. Job (Eds). *Australia's Adolescents: A Health Psychology Perspective.* Armidale: University of New England Press (pp 68-88).

Kenny, D.T. & Job, R.F.S. (Eds.) (1995). *Australia's adolescents: A health psychology perspective* (272 pages). Armidale: University of New England Press ISBN 1 875821 24 4.

(c) Child sexual abuse (CSA)

I provide expert reports on child complainants and alleged adult sex offenders to Joint Investigative Response Teams and Child Abuse Teams within the NSW Police. I have current experience:

(i) in counselling CSA victims.

(ii) providing structural and psychological analysis of CSA victim statements. I have developed specific expertise in the assessment of child testimony in sexual abuse cases.

(iii) reviewing video recordings of police interviews with alleged victims of CSA and providing commentary on the pertinent psychological issues.

(iv) providing expert statements and reviews of literature on matters pertaining to child development in general and CSA in particular, for the ODPP, Police, JIRT, barristers, and court.

(v) acting as an expert witness in cases of child sexual abuse, historical child sexual abuse, and paedophilia.

(vi) I have given evidence in court and have been cross-examined.

(vii) I have extensive knowledge of the child abuse literature and have written a book on the subject (see below).

(viii) I am able to provide comprehensive literature reviews on most subjects related to child sexual abuse.

(ix) I have publications – book, journal articles, monographs – on sex offending and have served on ministerial committees within the NSW Department of Juvenile Justice and the NSW Department of Corrective Services.

Key publications:

Kenny, D.T. (2018). *Children, sexuality, and child sexual abuse*. East Sussex, UK: Routledge**.**

This book has become a seminal text in the field because of its wide-ranging coverage and attention to all the recent research in the field, including the *Royal Commission into Institutional Responses to Child Sexual Abuse*. It covers all the key topics in child sexual abuse, including the nature of disclosures, both immediate and delayed, and their reliability; normal memory development and distortions of memory that can occur from a range of environmental influences including leading and suggestive interviewing; impacts of child sexual abuse, including short- and long-term consequences; assessment and forensic analysis of witness statements, and psychological analysis of CSA victim statements.

Kenny, D.T. (1997). Opinion, policy and practice in child sexual abuse: Implications for detection and reporting. In M. James (Ed.). *Paedophilia: Policy and prevention.* Research and Public Policy Series No 12: Australian Institute of Criminology, Sydney, Australia. ISSN 1326-6004. (pp 14-31).

In addition, last year I wrote a major report on paedophilia for the Child Abuse Squad, Ballina, addressing the question as to whether an individual in possession of child abuse material is a paedophile. This question had not been explicitly dealt with in the literature. Accordingly, I undertook major research on the subject and produced a report that the presiding judge allowed to be admitted into evidence to demonstrate tendency. The solicitor for the ODPP advised me that my report "may create a precedent for use in future similar matters."

(d) Juvenile offending and juvenile sex offending

For a number of years, I chaired or was a member of several committees within the NSW Department of Juvenile Justice and the New South Wales Department of Corrective Services, including Chair, Ministerial Steering Committee, NSW Department of Juvenile Justice Collaborative Research Unit, Chair, Research and Ethics Subcommittee, NSW Department of Juvenile Justice Collaborative Research Unit, Chair, Ministerial Steering Committee on Sexual Offending, New South Wales Department of Corrective Services, A/Chair and Member, Ministerial Reference Group on Sexual Offending, New South Wales Department of Corrective Services.

Kenny, D.T., Seidler, K., Keogh, T., & Blasczynski, A., (2000). Offence and clinical characteristics of Australian juvenile sex offenders. *Psychiatry, Psychology, and the Law, 7*, 2, 212-227.

Kenny, D.T., Keogh, T., & Seidler, K. (2001). Predictors of recidivism in Australian juvenile sex offenders. *Sexual Abuse: A Journal of Research and Treatment, 13*, 2, 131-148.

Kenny, D.T., & Nelson, P.K. (2008). *Young offenders on community orders: Health, welfare and criminogenic needs*. Sydney, Australia: Sydney University Press. ISBN 978-0-9804117-0-6.

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Kenny, D.T. (2015). Juvenile sex offenders in the criminal justice system. *Judicial Officers' Bulletin,* (Judicial Commission of NSW*), 27 (*4), 31-34.

(e) Educational psychology

During my earlier professional life, I worked as a school counsellor and specialist counsellor for emotionally disturbed children within the Division of Guidance and Special Education, NSW Department of Education. I was responsible for assessing children whose psychological difficulties were such that they could not be managed within the mainstream classroom. I undertook detailed assessments of their educational, social, and cognitive development in order to provide appropriate school placements for children who had significant trauma histories and intellectual disabilities.

Key publications:

Kenny, D.T. (2016). The adolescent brain: Implications for assessing young offenders' legal competence. *Judicial Officers' Bulletin* (Judicial Commission of NSW*), 28* (3), 23-27.

Kenny, D.T. (2012). Young offenders with an intellectual disability in the criminal justice system: Prevalence, profile, policy, planning and programming. *Judicial Officers' Bulletin (Judicial Commission of NSW),* 24, 5, 35-42.

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Kenny, D.T. & Frize, M. (2010). Intellectual disability, Aboriginal status and risk of re-offending in

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Kenny, D.T. (1989). The effect of grade repetition on the academic performance and social/emotional adjustment of infant and primary students. In Luszcz M. and Nettlebeck T. (Eds). *Psychological development: Perspectives across the lifespan*, pp 261-271. North Holland: Elsevier Science Publisher B.V.

(f) Family Therapy and Family Dispute Resolution

I assist parents to reach parenting agreements with respect to shared parental responsibility of their children following separation and divorce. I also undertake mediation with respect to property settlements. I undertook an 18-month training program with Relationships Australia in marriage and family therapy, in which capacity I work with families to resolve conflict, attachment ruptures, relationship stresses, and behavioural difficulties.

Having dual qualifications in both family therapy and family dispute resolution places me in an ideal position to assess families in custody disputes in relation to parenting capacity, shared parental responsibility and allegations of emotional, physical and sexual abuse. In these capacities I have provided parenting capacity reports to both family law solicitors and barristers, the Family Court and the Children's Court.

Key publication:

Kwok, E. & **Kenny, D.T.** (2015). The application of collaborative practice to misattributed paternity disputes. *Australasian Dispute Resolution Journal*, 26, 127- 136.

Other Major Consultancies, Invited Commissioned Reports and Invited Submissions to Government Inquiries

Kenny, D.T. (April, 2011). The NSW Law Reform Commission (NSW LRC). Consultation Paper 11. *Young people with cognitive and mental health impairments in the criminal justice system*, Roundtable.

Kenny, D.T. (2009). Submission on bullying to the NSW Legislative Council General Purpose Standing Committee No 2.

Kenny, D.T. & Lennings, C. (2007). *Provisional sentencing of serious young offenders.* NSW Sentencing Council. Department of the Attorney General.

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Allerton, M., Champion, U., Kenny, D.T., Butler, T. et al (2003). 2003 *Young people in custody health survey.* NSW Department of Juvenile Justice ISBN 0 7347 6518 5

Kenny, D.T. & Hunter, J. (2003). *Review of psychological services and specialist programs in the NSW*

Department of Juvenile Justice. Commonwealth Cost and Quality of Government (Internal Audit Bureau). (170 pages).

Kenny, D.T. (1996). *The effects of television/movie/video violence on the behaviour of children and adolescents*. Invited submission from the Australian Family Association (NSW Branch) to the Federal Government's Committee of Ministers on the 'Portrayal of Violence.'

Professional contributions in Psychology and the Law

Journal Reviewer

1. Frontiers in Psychology
2. Journal of Child Sexual Abuse
3. Sexual Abuse: A Journal of Research and Treatment
4. Psychology and the Law
5. International Journal of Offender Therapy and Comparative Criminology
6. Clinical Psychology Review
7. Journal of Sexual Abuse and Treatment
8. Behavioral and Brain Functions
9. Archives of Clinical Psychiatry
10. Australian Psychologist

Other invited presentations (selected)

Kenny, D.T. (2017). *Institutional Child Sexual Abuse*. Invited paper to the Local Court of NSW Annual Conference (2-7 August), Sydney, Australia.

Kenny, D.T. (2013). Young offenders in the juvenile justice system: A story of violence, intellectual disability, substance abuse, alienation and social disadvantage. Invited paper to *The Children's Court Magistrates' Section 16 meeting* (2 November). Sydney, Australia.

Kenny, D.T. (2011). Risks and needs of indigenous offenders: physical and mental health. Invited paper to A weekend conference for judicial officers and Aboriginal community members, *Judicial Commission of NSW* (10-11 September). Sydney, Australia.

Kenny, D.T. (2009). Intellectual disability and Indigenous status are predictors of recidivism in young offenders. Invited paper to the *Australian Institute of Criminology Conference* (1 September), Parramatta, Australia.

Kenny, D.T. (2009). Young offenders: the importance of compensatory attachments and the role of teachers. Keynote paper to the *NSW Department of Education Principals' Conference* (April), Sydney, Australia.

Kenny, D.T. (2007). Juvenile sex offenders: Theory into practice. Invited paper to the *Australian and New Zealand Association for the Treatment of Sex Abuse* (21 June). Blacktown, Sydney.

Kenny, D.T. (2007). Cognitive and educational problems of young offenders. *School Education Directors of Education Twilight Seminars* (26 June). Sydney, Australia.

Kenny, D.T. (2006). Physical and mental needs of young offenders. *Disability Strategic Group*, NSW Department of Juvenile Justice (August). Sydney, Australia.

Kenny, D.T**.** (2005). Impact of violence classification on its relationship to psychological factors and mental health. *Prisoner Health Research Symposium*, JusticeHealth (18 February). Sydney, Australia.

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Kenny, D.T., Keogh, T., & Seidler, K. (2001). Developmental and clinical characteristics of juvenile sex offenders: Predictors of recidivism and implications for treatment. *Inaugural Australian Forensic Psychology Conference* (February). Sydney, Australia.

Kenny, D.T. (1999). *Recidivism prediction model for juvenile sex offenders.* Invited presentation to the Minister for Juvenile Justice, Carmel Tebbutt MLC, and the Collaborative Research Unit, NSW Department of Juvenile Justice.

No. 22-11707

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

PAUL A. EKNES-TUCKER, et al.,
Plaintiffs-Appellees,

&

UNITED STATES OF AMERICA
Intervenor-Plaintiff-Appellee,

v.

GOVERNOR OF THE STATE OF ALABAMA, et al.,
Defendants-Appellants.

On Appeal from the United States District Court
for the Middle District of Alabama
Case No. 2:22-cv-184-LCB

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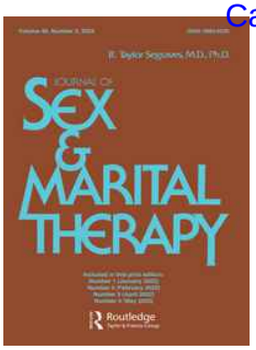

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REVIEW

Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults

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ABSTRACT

In less than a decade, the western world has witnessed an unprecedented rise in the numbers of children and adolescents seeking gender transition. Despite the precedent of years of gender-affirmative care, the social, medical and surgical interventions are still based on very low-quality evidence. The many risks of these interventions, including medicalizing a temporary adolescent identity, have come into a clearer focus through an awareness of detransitioners. The risks of gender-affirmative care are ethically managed through a properly conducted informed consent process. Its elements—deliberate sharing of the hoped-for benefits, known risks and long-term outcomes, and alternative treatments—must be delivered in a manner that promotes comprehension. The process is limited by: erroneous professional assumptions; poor quality of the initial evaluations; and inaccurate and incomplete information shared with patients and their parents. We discuss data on suicide and present the limitations of the Dutch studies that have been the basis for interventions. Beliefs about gender-affirmative care need to be separated from the established facts. A proper informed consent processes can both prepare parents and patients for the difficult choices that they must make and can ease professionals' ethical tensions. Even when properly accomplished, however, some clinical circumstances exist that remain quite uncertain.

KEYWORDS

Informed consent; ethics; gender dysphoria; gender identity; detransition

Introduction

Reconsideration of the meanings, purposes, indications, and processes of informed consent for transgender-identified youth is urgently needed. Parents of gender atypical children are considering social transition as early as preschool or grade school. Parents of preteens and teens are considering supporting their children's wishes to present in a new gender, take puberty blockers, cross-sex hormones, and plan for surgical alterations. College-aged youth are declaring new identities for the first time and obtaining hormones and surgery without their parents' knowledge.

When uncertain parents of children and teens consult their primary care providers, they are usually referred to specialty gender services. Parents and referring clinicians assume that specialists with "gender expertise" will undertake a thorough evaluation. However, the evaluations preceding the recommendation for gender transition are often surprisingly brief (Anderson & Edwards-Leeper, 2021) and typically lead to a recommendation for hormones and surgery, known as *gender-affirmative* treatment.

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Despite the widely recognized deficiencies in the evidence supporting gender-affirmative interventions (National Institute for Health & Care Excellence, 2020a; 2020b), the process of obtaining informed consent from patients and their families has no established standard. There is no consensus about the requisite elements of evaluations, nor is there unanimity about how informed consent processes should be conducted (Byne et al., 2012). These two matters are inconsistent from practitioner to practitioner, clinic to clinic, and country to country.

Social transition, hormonal interventions, and surgery have profound implications for the course of the lives of young patients and their families. It is incumbent upon professionals that these consequences be thoroughly, patiently clarified over time prior to undertaking any element of transition. The informed consent process does not preclude transition; it merely educates the family about the state of the science underpinning the decision to transition. Social transition, hormones, and surgeries are unproven in a strict scientific sense, and as such, to be ethical, require a thorough and fully informed consent process.

Ethical Concerns About Inadequate Informed Consent

The concept of informed consent in medicine has roots in both ethical theory and law. The ethical foundation is centered in the principles of beneficence, justice, and respect for autonomy, while the legal issues have to do with questions of malpractice (Katz et al., 2016).

Patients consenting to treatment must meet age-based and decisional capacity requirements (Katz et al., 2016). Minors less than the age of consent participate in decision-making by providing *assent*—an agreement with the intervention. The limited maturational cognitive capacities of minors are the key reason why parents serve as the ethical and legal surrogates for medical decision-making, tasked with signing an informed consent document (Grootens-Wiegers, Hein, van den Broek, & de Vries, 2017).

The informed consent process consists of three main elements: a disclosure of information about the nature of the condition and the proposed treatment and its alternatives; an assessment of patient and caregiver understanding of the information and capacity for medical decision-making; and obtaining the signatures that signify informed consent has been obtained (Katz et al., 2016). The current expectation that clinicians and institutions are required to thoroughly inform their patients about the benefits, risks, and uncertainties of a particular treatment, as well as about alternatives, has a long legal history in the United States (Lynch, Joffe, & Feldman, 2018).

Ethical concerns about inadequate informed consent for trans-identified youth have several potentially problematic sources, including *erroneous assumptions* held by professionals; *poor quality of the evaluation process*; and *incomplete and inaccurate information* that the patients and family members are given.

These concerns are amplified by the *dramatic growth* in demand for youth gender transition witnessed in the last several years that has led to a perfunctory informed consent process. A rushed process does not allow for a proper discussion of not only the benefits, but the profound risks and uncertainties associated with gender transition, especially when gender transition is undertaken before mature adulthood.

a. *Dramatic growth in demand for services threatens true informed consent*

Gender identity variations were thought to be extremely rare a generation ago. While the incidence in youth had not been officially estimated, in adults it was 2-14 per 100,000 (American Psychiatric Association, 2013, p. 454). However, around 2006, the incidence among youth began to rise, with a dramatic increase observed in 2015 (Aitken et al., 2015, de Graaf, Giovanardi, Zitz, & Carmichael, 2018). Currently, 2-9% of U.S. high school students now identify as transgender, while in colleges, 3% of males and 5% of females identify as gender-diverse (American College Health Association, 2021; Johns et al., 2019; Kidd et al., 2021).

Whereas previously most of the affected individuals identified as the opposite sex, there is now a growing trend toward identifying as *nonbinary*: neither male nor female or both male and female (Chew et al., 2020). A recent study reported that the majority of transgender-identifying youth (63%) now have a non-binary identity (Green, DeChants, Price, & Davis, 2021). Although the incidence of natal males asserting a trans identity in adolescence has significantly increased, the dramatic increase is driven primarily by the increase in natal females requesting services (Zucker, 2017). Many suffer from significant comorbid mental health disorders, have neurocognitive difficulties such as ADHD or autism or have a history of trauma (Becerra-Culqui et al., 2018; Kozlowska, McClure, et al., 2021).

The increase in rates of transgender identification is reflected in the numbers of youth seeking help from medical professionals. For example, according to data reported by the Tavistock gender clinic in the UK, in 2009, there were 51 requests for services (de Graaf et al., 2018); in 2019-2020, 2728 referrals were recorded—a 53-fold increase in just over a decade (Tavistock & Portman NHS Foundation Trust, 2020). The growing number of urban transgender health centers that have arisen in recent years (HRC, n.d.) reflects the increased demand for gender-related medical care among young people in North America Australia, and Europe.

This unprecedented increase has created pressure on institutions and practitioners to rapidly evaluate these youth and make recommendations about treatment. To respond to growing demand, an innovative *informed consent model of care* has been developed. Under this model, mental health evaluations are not required, and hormones can be provided after just one visit following the collection of a patient's or guardian's consent signature (Schulz, 2018). The provision of transition services under this model of care is available not just to those over 18, but for younger patients as well (Planned Parenthood League of Massachusetts, n.d.).

Although following the informed consent model of care for hormones and surgeries for youth may diminish clinicians' ethical or moral unease (Vrouenraets et al., 2020), we believe this model is the antithesis of true informed consent, as it jeopardizes the ethical foundation of patient autonomy. Autonomy is not respected when patients consenting to the treatment do not have an accurate understanding of the risks, benefits, and alternatives.

b. *Assumptions held by professionals influence the integrity of the informed consent process*

Gender dysphoric children and teens can intensely occupy the belief that their lives will be immensely improved by transition. Clinicians who have embraced the gender-affirmative model of care operate on the assumption that children and teens know best what they need to be happy and productive (Ehrensaft, 2017). These professionals, responding to the youths' passionate pleas, see their role as validating the young person's fervent wishes for hormones and surgery and clearing the path for gender transition. In doing so, they privilege the ethical principle of respect for patient autonomy (Clark & Virani, 2021) over their obligations for beneficence and non-maleficence.

Many of the gender-affirmative clinicians subscribe to the theory of *minority stress* – the supposition that the frequently co-occurring psychiatric symptoms of gender dysphoric individuals are a result of prejudice and discrimination brought about by gender non-conformity (Rood et al., 2016; Zucker, 2019), and that gender transition will ameliorate these symptoms. Some even claim that gender-affirmative care will successfully treat not only depression and anxiety but will also resolve neurocognitive deficits frequently present in gender dysphoric individuals (Turban, 2018; Turban, King, Carswell, & Keuroghlian, 2020; Turban & van Schalkwyk, 2018). These latter assertions have proven controversial even among the proponents of gender-affirmative interventions (Strang et al., 2018; van der Miesen, Cohen-Kettenis, & de Vries, 2018). The minority stress theory as the sole explanatory mechanism for co-occurring mental health illness has also been questioned in light of the evidence that psychiatric symptoms frequently pre-date the onset of gender dysphoria (Bechard, VanderLaan, Wood, Wasserman, & Zucker, 2017; Kaltiala-Heino, Sumia, Työläjärvi, & Lindberg, 2015; Kozlowska, Chudleigh, McClure, Maguire,

& Ambler, 2021). Other clinicians recognize the limits of gender-affirmative care and are aware that youth with underlying psychiatric issues are likely to continue to struggle post-transition (Kaltiala, Heino, Työläjärvi, & Suomalainen, 2020), but, unaware of alternative approaches such as gender-exploratory psychotherapy or watchful waiting (Bonfatto & Crasnow, 2018; Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019), these well-meaning professionals continue to treat youth with gender-affirmative interventions despite lingering doubts.

It is common for gender-affirmative specialists to erroneously believe that gender-affirmative interventions are a *standard of care* (Malone, D'Angelo, Beck, Mason, & Evans, 2021; Malone, Hruz, Mason, Beck, et al:, 2021). Despite the increasingly widespread professional beliefs in the safety and efficacy of pediatric gender transition, and the endorsement of this treatment pathway by a number of professional medical societies, the best available evidence suggests that the benefits of gender-affirmative interventions are of very low certainty (Clayton et al., 2021; National Institute for Health & Care Excellence, 2020a; 2020b) and must be carefully weighed against the health risks to fertility, bone, and cardiovascular health (Alzahrani et al., 2019; Biggs, 2021; Getahun et al., 2018; Hembree et al., 2017; Nota et al., 2019). Recently, emphasis has also been placed on psychosocial risks and as yet unknown medical risks (Malone, D'Angelo, et al., 2021).

Five scientific observations question and refute the assumption that an individual's experience of incongruence of sex and gender identity is best addressed by supporting the newly assumed gender identity with psychosocial and medical interventions.

1. The most foundational aspect of the diagnoses of "gender dysphoria" (DSM-5) and "gender incongruence" (ICD-11), requisite for the provision of medical treatment, is in flux, as professionals disagree on whether the presence of distress is a key diagnostic criterion, as stated in the DSM-5, or is irrelevant, as is the case according to the latest ICD-11 criteria (American Psychiatric Association, 2013; World Health Organization, 2019). Further, these diagnoses have never been properly field-tested (de Vries et al., 2021).
2. There are no randomized controlled studies demonstrating the superiority of various affirmative interventions compared to alternatives. There isn't even agreement about which outcome measures would be ideal in such studies.
3. There are few long-term follow-up studies of various interventions using predetermined outcome measures at designated intervals. Studies that have been conducted are, at best, inconsistent. Higher quality studies with longer-follow-up fail to demonstrate durable positive impacts on mental health (Bränström & Pachankis, 2020a; 2020b).
4. Rates of post-transition desistance, increased mental suffering, increased incidence of physical illness, educational failure, vocational inconstancy, and social isolation have not been established.
5. Numerous cross-sectional and prospective studies of transgender adults consistently demonstrate a high prevalence of serious mental health and social problems as well as suicide (Asscheman et al., 2011; Dhejne et al., 2011). Controversies about how to deal with trans-identified youth must consider the well described vulnerabilities of transgender adults.

It is equally important to realize that to date, research about alternative approaches, such as psychotherapy or watchful waiting, shares the scientific limitations of the research of more invasive interventions: there are no control groups, nor is there systematic follow-up at predetermined intervals with predetermined means of measurement (Bonfatto & Crasnow, 2018; Churcher Clarke & Spiliadis, 2019; Spiliadis, 2019). Parents and patients need to be informed of this as well.

Perhaps the single most problematic assumption held by some gender clinicians is that the young patients have simply been "born in the wrong body." This assumption seemingly frees clinicians from having to contend with the ethical dilemmas of recommending body-altering

interventions that are based on very low-quality evidence. Despite the principle of development that biology, psychosocial factors, and culture generate behavior, these clinicians may believe that atypical genders are created by biology. This reductionistic approach has been criticized repeatedly (Kendler, 2019).

While the origins of childhood or adolescent onset of gender incongruence have not yet been fully elucidated, brain studies of increasing technical sophistication have yet to demonstrate a distinct structure or pattern that accounts for an atypical gender identity, after statistically controlling for sexual orientation and exposure to exogenous hormones (Frigerio, Ballerini, & Valdés Hernández, 2021). Twin studies also demonstrate that while biology plays a role in one's experience of "gender incongruence," it is far from deterministic (Diamond, 2013).

A growing number of clinicians and researchers are noting that the dramatic rise of teens declaring a trans identity appears to be, at least in part, a result of peer influence (Anderson, 2022; Hutchinson, Midgen, & Spiliadis, 2020 Littman, 2018; Littman, 2020; Zucker, 2019). Some have noted yet another influx of trans-identified youth emerging during the COVID lockdowns, and have hypothesized that increased isolation coupled with heavy internet exposure may be responsible (Anderson, 2022). While the research into the phenomenon of social influence as a contributor to trans identification of youth is still in its infancy, the possibility that clinicians are providing treatments with permanent consequences to address what may be transient identities in youth poses a serious ethical dilemma.

c. *Poor evaluations*

There is a growing recognition that rapid evaluations which disregard factors contributing to the development of gender dysphoria in youth are problematic. In November 2021, two leaders of the World Professional Organization for Transgender Health (WPATH) warned the medical community that the "The mental health establishment is failing trans kids" (Anderson & Edwards-Leeper, 2021). Frequently, evaluations provided by gender clinicians may only ascertain the diagnosis of *gender dysphoria* (DSM-5) or its ICD-11 counterpart *gender incongruence*, and screen for conspicuous mental illness prior to recommending hormones and surgeries. These limited, abbreviated evaluations overlook, and as a result fail to address, the relevant issue of the forces that may have influenced the young person's current gender identity.

Confirming the young person's self-diagnosis of gender dysphoria or gender incongruence is easy. Clarifying the developmental forces that have influenced it and determining an appropriate intervention are not. Contextualizing these forces involves an understanding of child and adolescent developmental processes, childhood adversity, co-existing physical and cognitive disadvantages, unfortunate parental or family circumstances (Levine, 2021), as well as the role of social influence (Anderson, 2022; Anderson & Edwards-Leeper, 2021; Littman, 2018; 2021).

The poor quality of mental health evaluations has been a point of significant discontent for a growing number of parents of gender dysphoric youth. Increasingly, parents have formed dozens of support groups in North America, Europe, Australia and New Zealand, united in their objections to the idea that the best or the only treatment for their gender dysphoric children is affirmation (Genspect, 2021). These distressed parents, recognizing that their son or daughter may eventually decide to present to others as a trans person, want a psychotherapeutic investigation to understand what contributed to the development of this identity and an exploration of noninvasive treatment options. Frequently, they cannot find anyone in their community who does not recommend immediate affirmation.

The American Academy of Pediatrics' Committee of Bioethics recognizes that "parents…are better situated than others to understand the unique needs of their children and to make appropriate, caring decisions regarding their children's health care" (Katz et al., 2016). The plight of the families unable to find specialists capable of conducting thorough evaluations draws attention to the widespread acceptance of medical interventions for gender-dysphoric youth as the first line of treatment. The problem is that such care has been established through precedent rather

than through scientific demonstrations of its efficacy. We contend that parents and patients have a right to know this, and that it is the professionals' responsibility and obligation to inform them of the state of knowledge in this arena of care.

d. *Incorrect information shared*

In sharing the information with patients and families, two key areas of uncertainty must be emphasized. The first one is the uncertain permanence of a child's or an adolescent's gender identity (Littman, 2021; Ristori & Steensma, 2016; Singh, Bradley, & Zucker, 2021; Vandenbussche, 2021; Zucker, 2017). The second is the uncertain long-term physical and psychological health outcomes of gender transition (National Institute for Health & Care Excellence, 2020a; 2020b). Unfortunately, gender specialists are frequently unfamiliar with, or discount the significance of, the research in support of these two concepts. As a result, the informed consent process rarely adequately discloses this information to patients and their families.

Problematically, it is common for gender clinicians to emphasize the risk of suicide if a young person's wish to transition gender is not immediately fulfilled. There is a significant amount of misinformation surrounding the question of suicidality of trans-identified youth (Biggs, 2022). Providers of gender-affirmative care should be careful not to unwittingly propagate misinformation regarding suicide to parents and youths. They should also be reminded that any conversations about suicide should be handled with great care, due to its socially contagious nature (Bridge et al., 2020; HHS, 2021).

i. High Rate of desistance/natural resolution of gender dysphoria in children is not disclosed

There have been eleven research studies to date indicating a high rate of resolution of gender incongruence in children by late adolescence or young adulthood without medical interventions (Cantor, 2020; Ristori & Steensma, 2016; Singh et al., 2021). An attempt has been made to discount the applicability of this research, suggesting that the studies were based on merely gender non-conforming, rather than truly gender-dysphoric, children (Temple Newhook et al., 2018). However, a reanalysis of the data prompted by this critique confirmed the initial finding: Among children meeting the diagnostic criteria for "Gender Identity Disorder" in DSM-IV (currently "Gender Dysphoria in DSM-5), 67% were no longer gender dysphoric as adults; the rate of natural resolution for gender dysphoria was 93% for children whose gender dysphoria was significant but subthreshold for the DSM diagnosis (Zucker, et al., 2018). It should be noted that high resolution of childhood-onset gender dysphoria had been recorded before the practice of social transition of young children was endorsed by the American Academy of Pediatrics (Rafferty et al., 2018). It is possible that social transition will predispose a young person to persistence of transgender identity long-term (Zucker, 2020).

The information regarding the resolution of gender dysphoria among those with adolescent-onset gender dysphoria, which is currently the predominant presentation, is less clear. A growing body of evidence suggests that for many teens and young adults, a post-pubertal onset of transgender identification can be a transient phase of identity exploration, rather than a permanent identity, as evidenced by a growing number of young detransitioners (Entwistle, 2020; Littman, 2021; Vandenbussche, 2021). Previously, the rate of detransition and regret was reported to be very low, although these estimates suffered from significant limitations and were likely undercounting true regret (D'Angelo, 2018). However, in the last several years since gender-affirmative care has become popularized, the rate of detransition appears to be accelerating.

According to a recent study from a UK adult gender clinic, 6.9% of those treated with gender-affirmative interventions detransitioned within only 16 months of starting treatment, and another 3.4% had a pattern of care suggestive of detransition, yielding a rate of probable detransition in excess of 10%. Another 21.7% of patients disengaged from the clinic without completing

their treatment plan (Hall, Mitchell, & Sachdeva, 2021). While some of these individuals later reengaged with the gender service, the authors concluded, "detransitioning might be more frequent than previously reported." Another study from a UK primary care practice found that 12.2% of those who had started hormonal treatments either detransitioned or documented regret, while the total of 20% stopped the treatments for a wider range of reasons. The mean age of their presentation with gender dysphoria was 20, and the patients had been taking gender-affirming hormones for the average 5 years (17 months-10 years) prior to discontinuing.

Comparing these much higher rates of treatment discontinuation and detransition to the significantly lower rates reported by the older studies, the researchers noted: "Thus, the detransition rate found in this population is novel and questions may be raised about the phenomenon of overdiagnosis, overtreatment, or iatrogenic harm as found in other medical fields" (Boyd, Hackett, & Bewley, 2022 p.15). Indeed, given that regret may take up to 8-11 years to materialize (Dhejne, Öberg, Arver, & Landén, 2014; Wiepjes et al., 2018), many more detransitioners are likely to emerge in the coming years. Detransitioner research is still in its infancy, but two recently published studies examining detransitioner experiences report that detransitioners from the recently-transitioning cohorts feel they had been rushed to medical gender-affirmative interventions with irreversible effects, often without the benefit of appropriate, or in some instances any, psychologic exploration (Littman, 2021; Vandenbussche, 2021).

Clinicians should also disclose to patients and parents that there is no test which can accurately predict who will persist in their transgender identification upon reaching mature adulthood (Ristori & Steensma, 2016). Families should be made aware that a period of strong cross-sex identification in childhood is commonly associated with future homosexuality (Korte et al., 2008). Research in desistance confirms that the majority of youth whose gender dysphoria resolves naturally do indeed grow up to be gay, lesbian, or bisexual adults (Cantor, 2020, Appendix; Singh et al., 2021).

ii. Implications of very low-quality evidence that underlies the practice of pediatric gender transition are not explained

The quality of evidence underlying the practice of pediatric gender transition is widely recognized to be of very low quality (Hembree et al., 2017). In 2020, the most comprehensive systematic review of evidence to date, commissioned by the UK National Health System (NHS) and conducted by the National Institute for Health and Care Excellence (NICE), concluded that the evidence for both puberty blocking and cross-sex hormones is of very low certainty (National Institute for Health & Care Excellence, 2020a; 2020b).

According to the NICE review of evidence for puberty blockers, the studies "are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as assessed using modified GRADE [Grading of Recommendations, Assessment, Development and Evaluations]. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly" (National Institute for Health & Care Excellence, 2020a, p.13). NICE reached similar conclusions regarding the quality of the evidence for cross-sex hormones (National Institute for Health & Care Excellence, 2020b).

Problematically, the implications of administering a treatment with irreversible, life-changing consequences based on evidence that has an official designation of "very low certainty" according to modified GRADE is rarely discussed with the patients and the families. GRADE is the most widely adopted tool for grading the quality of evidence and for making treatment recommendations worldwide. GRADE has four levels of evidence, also known as certainty in evidence or quality of evidence: very low, low, moderate, and high (BMJ Best Practice, 2021). When evidence is assessed to be "very low certainty," there is a high likelihood that the patients will not experience the effects of the proposed interventions (Balshem et al., 2011).

In the context of providing puberty blockers and cross-sex hormones, the designation of "very low certainty" signals that the body of evidence asserting the benefits of these interventions is

highly unreliable. In contrast, several negative effects are quite certain. For example, puberty blockade followed by cross-sex hormones leads to infertility and sterility (Laidlaw, Van Meter, Hruz, Van Mol, & Malone, 2019). Surgeries to remove breasts or sex organs are irreversible. Other health risks, including risks to bone and cardiovascular health, are not fully understood and are uncertain, but the emerging evidence is alarming (Alzahrani et al., 2019; Biggs, 2021).

iii. The question of suicide is inappropriately handled

Suicide among trans-identified youth is significantly elevated compared to the general population of youth (Biggs, 2022; de Graaf et al., 2020). However, the "transition or die" narrative, whereby parents are told that their only choice is between a "live trans daughter or a dead son" (or vice-versa), is both factually inaccurate and ethically fraught. Disseminating such alarmist messages hurts the majority of trans-identified youth who are not at risk for suicide. It also hurts the minority who are at risk, and who, as a result of such misinformation, may forgo evidence-based suicide prevention intervention in the false hopes that transition will prevent suicide.

The notion that trans-identified youth are at alarmingly high risk of suicide usually stems from biased online samples that rely on self-report (D'Angelo et al., 2020; James et al., 2016; The Trevor Project, 2021), and frequently conflates suicidal thoughts and non-suicidal self-harm with serious suicide attempts and completed suicides. Until recently, little was known about the actual rate of suicide of trans-identified youth. However, a recent analysis of data from the biggest pediatric gender clinic in the world, the UK's Tavistock, found the rate of completed youth suicides to be 0.03% over a 10-year period, which translates into the annual rate of 13 per 100,000 (Biggs, 2022). While this rate is significantly elevated compared to the general population of teens, it is far from the epidemic of trans suicides portrayed by the media.

The "transition or die" narrative regards suicidal risk in trans-identified youth as a different phenomenon than suicidal risk among other youth. Making them an exception falsely promises the parents that immediate transition will remove the risk of suicidal self-harm. Trans patients themselves complain about the so-called "trans broken arm syndrome" – a frustrating pattern whereby physicians "blame" all the problems the patients are experiencing on their trans status, and a result, fail to perceive and respond to other sources of distress (Paine, 2021). Clinicians caring for trans-identified youth should be reminded that suicide risk in all patients is a multi-factorial phenomenon (Mars et al., 2019). To treat trans youths' suicidality as an exception is to deny them evidence-based care.

A recent study of three major youth clinics concluded that suicidality of trans-identifying teens is only somewhat elevated compared to that of youth referred for mental health issues unrelated to gender identity struggles (de Graaf et al., 2020). Another study found that transgender-identifying teens have relatively similar rates of suicidality compared to teens who are gay, lesbian and bisexual (Toomey, Syvertsen, & Shramko, 2018). Depression, eating disorders, autism spectrum conditions, and other mental health conditions commonly found in transgender-identifying youth (Kaltiala-Heino, Bergman, Työläjärvi, & Frisen, 2018; Kozlowska, McClure, et al., 2021; Morandini, Kelly, de Graaf, Carmichael, & Dar-Nimrod, 2021) are all known to independently contribute to the probability of suicide (Biggs, 2022; Simon & VonKorff, 1998; Smith, Zuromski, & Dodd, 2018).

The "transition or suicide" narrative falsely implies that transition will prevent suicides. Clinicians working with trans-identified youth should be aware that although in the short-term, gender-affirmative interventions can lead to improvements in some measures of suicidality (Kaltiala et al., 2020), neither hormones nor surgeries have been showed to reduce suicidality in the long-term (Bränström & Pachankis, 2020a; 2020b). Alarmingly, a longitudinal study from Sweden that covered more than a 30-year span found that adults who underwent surgical transition were 19 times more likely than their age-matched peers to die by suicide overall, with female-to-male participants' risk 40 times the expected rate (Dhejne et al., 2011, Table S1).

Another key longitudinal study from the Netherlands concluded that suicides occur at a similar rate at all stages of transition, from pretreatment assessment to post-transition follow-up (Wiepjes et al., 2020). The data from the Tavistock clinic also did not show a statistically significant difference between completed suicides in the "waitlist" vs. the "treated" groups (Biggs, 2022). Luckily, in both groups, completed suicides were rare events (which may have been responsible for the lack of statistical significance). Thus, we consider the "transition or die" narrative to be misinformed and ethically wrong.

In our experience in working with trans-identified youth, an adolescent's suicidality can sometimes arise as a response to parental distress, resistance, skepticism, or wish to investigate the forces shaping the new gender identity before social transition and hormone therapy. When mental health professionals or other healthcare providers fail to recognize the legitimacy of parental concerns, or label the parents as transphobic, this only tends to intensify intrafamilial tension. Clinicians would be well-advised that gender transition is not an appropriate response to suicidal intent or threat, as it ignores the larger mental health and social context of the young patient's life—the entire family is often in crisis. Trans-identified adolescents should be screened for self-harm and suicidality, and if suicidal behaviors are present, an appropriate evidence-based suicide prevention plan should be put in place (de Graaf et al., 2020).

The Dutch Study: the questionable basis for the gender affirmative model of care for youth

Few practitioners of gender-affirmative interventions, and even fewer patients and families, realize that the foundation of the practice of medically transitioning minors stems from a single Dutch proof of concept study, the outcomes of which were documented in two studies (de Vries, Steensma, Doreleijers, Cohen, & Kettenis, 2011; de Vries et al., 2014). The former (de Vries et al., 2011) reported on cases who underwent puberty blockade, while the latter (de Vries et al., 2014) reported on a subset of the cases who completed surgeries.

The Dutch study subjects' high level of psychological functioning at 1.5 years after surgery, which was the study end point, was an impressive feat. However, both of the studies suffer from a high risk of bias due to their study design, which is effectively a non-randomized case series—one of the lowest levels of evidence (Mathes & Pieper, 2017; National Institute for Health & Care Excellence, 2020a). In addition, the studies suffer from limited applicability to the populations of adolescents presenting today (de Vries, 2020). The interventions described in the study are currently being applied to adolescents who were not cross-gender identified prior to puberty, who have significant mental health problems, as well as those who have non-binary identities—all of these presentations were explicitly disqualified from the Dutch protocol. Despite these limitations, the Dutch clinical experiment has become the basis for the practice of medical transition of minors worldwide and serves as the basis for the recommendations outlined in the 2017 Endocrine Society guidelines (Hembree et al., 2017).

We contend that the Dutch studies have been misunderstood and misrepresented as providing evidence of the safety and efficacy of these interventions for all youth. It is important that both the strengths and the weaknesses of these two studies are understood, as to date, the Dutch experience presents the best available evidence behind the practice of pediatric gender transition.

Rationale for pediatric transition

Prior to the 1990s, gender transitions were typically initiated in mature adults (Dhejne et al., 2011). However, it was noted that particularly for natal male patients, hormonal and surgical interventions failed to achieve satisfactory results, and patients had a "never disappearing masculine appearance" (Delemarre-van de Waal & Cohen-Kettenis, 2006). The lack of adequate cosmetic outcomes was thought to contribute to the frequently disappointing outcomes of medical

gender transition, with persistently high rates of mental illness and suicidality post-transition (Delemarre-van de Waal & Cohen-Kettenis, 2006; Dhejne et al., 2011; Ross & Need, 1989).

In the mid 1990s, a team of Dutch researchers hypothesized that by carefully selecting a subset of gender dysphoric children who would likely be transgender-identified for the rest of their lives, and by medically intervening before puberty left an irreversible mark on their bodies, the cosmetic outcomes would be improved—and as a result, mental health outcomes might be improved (Gooren & Delemarre-van de Waal, 1996).

Mixed study findings

In 2014, the Dutch research team published a key longitudinal study of mental health outcomes of 55 youths who completed medical and surgical transition (de Vries et al., 2014). The 2014 paper (sometimes referred to as the "Dutch study") reported that for youth with severe gender dysphoria that started in early childhood and persisted into mid-adolescence, a sequence of puberty blockers, cross-sex hormones, and breast and genital surgeries (including a mandatory removal of the ovaries, uterus and testes), with ongoing extensive psychological support, was associated with positive mental health and overall function 1.5 years post-surgery.

While the Dutch reported resolution of gender dysphoria post-surgery in study subjects, the reported psychological improvements were quite modest (de Vries et al., 2014). Of the 30 psychological measurements reported, nearly half showed no statistically significant improvements, while the changes in the other half were marginally clinically significant at best (Malone, D'Angelo, et al., 2021). The scores in anxiety, depression, and anger did not improve. The change in the Children's Global Assessment Scale, which measures overall function, was one of the most impressive changes—however it too remained in the same range before and after treatment (de Vries et al., 2014).

Problematic discordance between reduced gender dysphoria and lack of meaningful improvements in psychological measures

The discordance between the marked reduction in gender dysphoria, as measured by the UGDS (Utrecht Gender Dysphoria Scale), and the lack of meaningful changes in psychological function using standard measures, warrants further examination. There are three plausible explanations for this lack of agreement. Any one of these three explanations calls into question the widely assumed notion that the medical interventions significantly improve mental health or lessen or eradicate gender dysphoria.

One possible explanation is that gender dysphoria as measured by UGDS, and psychological function, as measured by most standard instruments, are not correlated. This contradicts the primary rationale for providing gender-affirmative treatments for youth (which is to improve psychological health and functioning), and if true, ethically threatens these medical interventions. The other plausible explanation stems from the high psychological function of all the subjects at baseline; the subjects were selected because they were free from significant mental health problems (de Vries et al., 2014). As a result, there was little opportunity to meaningfully improve. This explanation highlights a key limitation in applying the study's results to the majority of today's gender dysphoric youth, who often present with a high burden of mental illness (Becerra-Culqui et al., 2018; Kozlowska, McClure, et al., 2021). The study cannot be used as evidence that these procedures have been proven to improve depression, anxiety, and suicidality.

A third possible explanation for the discordance between only minor changes in psychological outcomes but a significant drop in gender dysphoria comes from a close examination of the UGDS scale itself and how it was used by the Dutch researchers. This 12-item scale, designed by the Dutch to assess the severity of gender dysphoria and to identify candidates for hormones

and surgeries, consists of "male" (UGDS-aM) and "female" (UGDS-aF) versions (Iliadis et al., 2020). At baseline and after puberty suppression, biological females were given the "female" scale, while males were given the "male" scale. However, post-surgery, the scales were flipped: biological females were assessed using the "male" scale, while biological males were assessed on the "female" scale (de Vries et al., 2014). We maintain that this handling of the scales may have at best obscured, and at worst, severely compromised the ability to meaningfully track how gender dysphoria was affected throughout the treatment.

Consider this example. At baseline, a gender dysphoric biological female would rate items from the "female" scale such as: "I prefer to behave like a boy" (item 1); "I feel unhappy because I have to behave like a girl" (item 6) and "I wish I had been born a boy" (item 12). Positive answers to these questions would have contributed to a high baseline gender dysphoria score. After the final surgery, however, this same patient would be asked to rate items from the "male" scale, including the following: "My life would be meaningless if I had to live as a boy" (item 1); "I hate myself because I am a boy" (item 6) and "It would be better not to live than to live as a boy" (item 12). A gender dysphoric female would not endorse these statements (at any stage of the intervention), which would lead to a lower gender dysphoria score.

Thus, the detected drop in the gender dysphoria scores for biological males and females may have had less to do with the success of the interventions, and more to do with switching the scale from the "female" to the "male" version (and vice-versa) between the baseline and post-surgical period. This, too, may explain why no changes in gender dysphoria were noted between baseline and the puberty blockade phase, and were only recorded after the final surgery, when the scale was switched.

It must be considered that had the researchers administered the "flipped" scale earlier, at the completion of the puberty blocker stage, UGDS scale could have registered the reduction in gender dysphoria. Likewise, however, one must consider the possibility that had *both sets of scales* been administered to the same individual at baseline, a "reduction" in gender dysphoria could have been registered upon switching of the scale, *well before any interventions began*. The question here is whether the diminishment of quantitative measures of gender dysphoria is largely an artifact of what scale was used.

It must be noted that the UGDS measure has been demonstrated only to effectively differentiate between clinically referred gender dysphoric individuals, non-clinically referred controls, and participants with disorders of sexual development, and was not designed to detect changes in gender dysphoria during treatment (Steensma, McGuire, Kreukels, et al. 2013). The presence of items such as "I dislike having erections" (item 11, UGDS-aM), which would have to be rated by birth-females, and "I hate menstruating because it makes me feel like a girl (item 10, UGDS-aF), which would be presented to birth-males, neither of which could be meaningfully rated by either at any stage of the interventions, further illustrates that UGDS has questionable validity for the purpose of detecting meaningful changes in gender dysphoria as a result of medical and surgical treatment.

The updated UGDS scale (UGDS-GS), developed by the Dutch after the publication of their seminal study, has eliminated the two-sex version of the scale in favor of a single battery of questions applicable to both sexes (McGuire et al., 2020). This change may lead to a more reliable measurement of treatment-associated changes in future research. Other gender dysphoria scales also exist (Hakeem, Črnčec, Asghari-Fard, Harte, & Eapen, 2016; Iliadis et al., 2020) and may or may not be better suited for the purposes of measuring the impact of medical interventions on underlying gender distress. Gender dysphoria, of course, may also prove to be a more complex concept than can be measured by any scale.

Other limitations

The two Dutch studies were conducted without a control group (de Vries et al., 2011; de Vires et al., 2014). Nor could the researchers control for mental health interventions, which all the

subjects received in addition to hormones and surgery. The Dutch only evaluated mental health outcomes and did not assess physical health effects of hormones and surgery. The sample size was small: the final study reported the outcomes of only 55 children, and as few as 32 were evaluated on key measures of psychological outcomes.

It is important to realize that the Dutch sample was carefully selected, which introduced a source of bias, and also challenges the study's applicability. From the 196 adolescents initially referred, 111 were considered eligible to start puberty blockers, and of this group, only the 70 most mature and mentally stable who proceeded to cross-sex hormones were included in the study (de Vries et al., 2011). Of note, 97% of the selected cases were attracted to members of their natal sex at baseline. All were cross-sex identified, with no cases of non-binary identities. The final study only followed 55, rather than the original 70 cases, further excluding from reporting the outcomes of subjects who had experienced adverse events, including: one death from surgery-related complications and three cases of complications such as obesity and diabetes that rendered subjects ineligible for surgery. Three more subjects refused to be contacted or dropped out of care, which may mask adverse outcomes (de Vries et al., 2014).

There is no knowledge of the fate of 126 patients who did not participate in the Dutch study. Longer term outcomes of the subjects who did participate are lacking. We are aware of only one case of long-term follow-up for a female-to-male patient treated by the Dutch team in the 1990s. The case study describing the subject's functioning at the age of 33 found that the patient did not regret gender transition. However, he reported struggling with significant shame related to the appearance of his genitals and to his inability to sexually function; had problems maintaining long-term relationships; and experienced depressive symptoms (Cohen-Kettenis, Schagen, Steensma, de Vries, & Delemarre-van de Waal, 2011). Notably, these problems had not yet emerged when the same patient was assessed at the age of 20, when he reported high levels of satisfaction in general, and was "very satisfied with the results [of the metoidioplasty]" in particular (Cohen-Kettenis & van Goozen, 1998, p.248). Since the last round of psychological outcomes of the individuals in the Dutch study was obtained when the subjects were around 21 years of age (de Vries et al., 2014), it raises questions how they will fair in during the decade when new developmental tasks, such as, career development, forming long-term intimate relationships and friendships, or starting families come into focus.

As to the unknown outcomes of the patients rejected by the Dutch protocol, one study did report on 14 adolescents who sought gender reassignment in the same clinic, but were disqualified from treatment due to "psychological or environmental problems" (Smith, Van Goozen, & Cohen-Kettenis, 2001, p. 473). The study found that at follow-up 1-7 years after the original application, 11 of the 14 no longer wished to transition, and 2 others only slightly regretted not transitioning (Malone, D'Angelo, et al., 2021; Smith et al., 2001). This further underscores the importance of conducting research utilizing control groups and following the subjects for an extended period.

A recent attempt to replicate the results of the first Dutch study (de Vries et al., 2011) found no demonstrable psychological benefit from puberty blockade, but did find that the treatment adversely affected bone development (Carmichael et al., 2021). The final Dutch study (de Vries et al., 2014) has never been attempted to be replicated with or without a control group.

The scaling of the Dutch Protocol beyond original indications

The medical and surgical sequence of Dutch protocol has been aggressively scaled worldwide without the careful evaluations and vetting practiced by the Dutch. The protocol's original investigators have recently expressed concern that the interventions they described have been widely adopted on four continents without several of the protocol's essential discriminatory features (de Vries, 2020).

The extensive multi-year multidisciplinary evaluations of the children have been abbreviated or simply bypassed. The medical sequence is routinely used for children with post-pubertal onset of transgender identities complicated by mental health comorbidities (Kaltiala-Heino et al., 2018), and not just for those high-functioning adolescents with persistent early life cross-identifications, as was required by the Dutch protocol (de Vries & Cohen-Kettenis, 2012). Further, it has become increasingly common to socially transition children before puberty (Olson, Durwood, DeMeules, & McLaughlin, 2016), even though this was explicitly discouraged by the Dutch protocol at the time (de Vries & Cohen-Kettenis, 2012).

In addition, medical transition is frequently initiated much earlier than recommended by the original protocol (de Vries & Cohen-Kettenis, 2012). The authors of the protocol were aware that most children would have a spontaneous realignment of their gender identity with sex by going through early- to mid-stages of puberty (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008). The average age of initiating puberty blockade in the Dutch study was around 15. In contrast, currently the age limit has been lowered to the age of Tanner stage II, which can occur as early as 8-9 years (Hembree et al., 2017). Irreversible cross-sex hormones, initiated in the Dutch study at the average age of nearly 17, are currently commonly prescribed to 14-year-olds, and this lower age threshold has been recommended by draft recommendation by WPATH Standards of Care 8, the final version of which is due to be released in early 2022. The fact that children are transitioned before their identity is tested against the biological reality and before natural resolution of gender dysphoria has had a chance to occur is a major deviation from the original Dutch protocol. Systematic follow-up, reassessments, and tracking and publishing of outcomes are not performed.

As the lead Dutch researchers have begun to call for more research into the novel presentation of gender dysphoria in youth (de Vries, 2020; Voorzij, 2021) and question the wisdom of applying the hormonal and surgical treatment protocols to the newly presenting cases, many recently educated gender specialists mistakenly believe that the Dutch protocol proved the concept that its sequence helps all gender-dysphoric youth. Although aware of the Dutch study's importance, they seem to be unaware of its agreed upon limitations, and the Dutch clinicians' own discomfort that most new trans-identified adolescents presenting for care today significantly differ from the population the Dutch had originally studied. These facts, of course, underscore the need for a robust informed consent process.

The recommendations for informed consent process for children, adolescents, and young adults

Consent for all stages of gender transition should be explicit, not implied

Noninvasive medical care or care that carries little risk of harm does not require a signed informed consent document; rather, consent is implied through the act of a patient presenting for care. For example, when a parent brings in a child for a skin laceration or abscess, consent for sutures or simple incision and drainage is implied. Similarly, when a child presents with pneumonia and is hospitalized, consent for chest x-ray, IV fluids, and antibiotics is also implied. It is assumed that patients or their guardians agree to the interventions and understand the benefits and risks. When risks are greater, such as prior to surgery, chemotherapy, or another invasive procedure, an informed consent document is signed. Such situations require an explicit, or express informed consent.

In the context of interventions for gender dysphoria or gender incongruence, the uncertainties associated with puberty blocking, cross-sex hormones, and gender-affirmative surgeries are well-recognized (Manrique et al., 2018; National Institute for Health & Care Excellence, 2020a; 2020b; Wilson et al., 2018). In these cases, consent should be explicit rather than implied because of the complexity, uncertainty, and risks involved.

Informed consent for social transition represents a gray area. Evidence suggests that social transition is associated with the persistence of gender dysphoria (Hembree et al.,

2017; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013). This suggests that social gender transition is a form of a psychological intervention with potential lasting effects (Zucker, 2020). While the causality has not been proven, the possibility of iatrogenesis and the resulting exposure to the risks of future medical and surgical gender dysphoria treatments, qualifies social gender transition for explicit, rather than implied, consent.

Full unbiased disclosure of benefits, risks and alternatives is requisite

When mental health professionals are involved in evaluations and recommendations, the informed consent process begins either as part of an extended evaluation or is integrated in a psychotherapeutic process, separately or together, with the parents and patient. When pediatricians, nurse practitioners, or primary care physicians perform the initial evaluation, the informed consent process is more likely to be labeled as such in a briefer series of meetings.

In all settings, the informed consent discussions for gender-affirmative care should include three central ideas:

1. The decision to initiate gender transition may predispose the child to persist in their transgender identity long-term.
2. Many of the physical changes contemplated and undertaken are irreversible.
3. Careful long-term studies have not been done to verify that these interventions enable better physical and mental health or improved social functioning, or that they do not cause harm.

The informed consent process, culminating with a signed document, signifies that parents and patient have been educated about the short- and long-term risks, benefits and uncertainties associated with all relevant stages of the gender-affirmative interventions. The process must also inform the patients and families about the full range of alternative treatments, including the choice of not socially or medically treating the child's or adolescent's current state of gender/body incongruence.

Decisional capacity to consent needs to be assessed and family should be involved

Trans-identified youth typically present themselves as strongly desiring hormones and ultimately, surgery. It should not be assumed that their eagerness is matched with the capacity to carefully consider the consequences of their realized desires. Trans-identified youth younger than the age of consent should be part of the informed consent process, but they may not be mature enough to recognize or admit their concerns about the proposed intervention. For this reason, it is the parents who, after careful consideration, are responsible for signing an informed consent document.

The issue of the exact age at which adolescents are mature enough to consent to gender transition has proven contentious: courts have been asked to decide about competence to consent to gender-affirmative hormones for youth in the United Kingdom and Australia (Ouliaris, 2021). In the United States, the legal age for medical consent for gender-affirmative interventions varies by state.

When patients are age 18 and older, and in some jurisdictions as young as age 15 (Right to medical or dental treatment without parental consent, 2010), they do not legally require parental approval for medical procedures. But because an individual's change of gender has profound implications for parents, siblings, and other family members, it is usually prudent for clinicians to seek their input directly or indirectly during the informed consent process. This is done by requesting a meeting with the parents.

A recent study by a Dutch research team attempted to evaluate the decisional capacity of adolescents embarking on gender transition (Vrouenraets, de Vries, de Vries, van der Miesen, & Hein, 2021). The researchers administered the MacCAT-T tool, comprised of the *understanding*, *appreciating*, *reasoning*, and *expressing a choice* domains, to 74 adolescents who were 14.7 years old on average (with the minimum age of 10). They concluded that the adolescents were competent to consent for starting pubertal suppression, calling for similar research for the <12 group, particularly because "birth-assigned girls … may benefit from puberty suppression as early as 9 years of age" (Vrouenraets et al., 2021 p.7).

This study suffers from two significant limitations involving the MacCAT-T tool. It was never designed for children. Rather, it was designed to assess medical consent capacities of adults suffering from conditions such as dementia, schizophrenia, and other psychiatric disorders. There is a fundamental lack of equivalency between consenting to treatment by adults with cognitive impairments and obtaining consent from healthy children whose age-appropriate cognitive capacities are intact, but who lack the requisite life experiences to consent to profound life-changing medical interventions. We doubt, for example, whether even highly intelligent children who have not had sexual experiences can meaningfully comprehend the loss of future sexual function and reproductive abilities.

In addition, even for adults, the MacCAT-T tool has been criticized for its exclusive focus on cognitive aspects of capacity, failing to account for the non-cognitive aspects such as values, emotions and other biographic and context specific aspects inherent in the complexity of the decision process in real life (Breden & Vollmann, 2004). Children's values and emotions undergo tremendous change during the process of maturation.

The authors' conclusion about their young patients' competence to consent should be compared with what a panel of judges wrote in the challenge to the Tavistock treatment protocol (Bell v Tavistock, 2020):

> …the clinical intervention we are concerned with here is different in kind to other treatments or clinical interventions. In other cases, medical treatment is used to remedy, or alleviate the symptoms of, a diagnosed physical or mental condition, and the effects of that treatment are direct and usually apparent. The position in relation to puberty blockers would not seem to reflect that description. [para 135]

> …we consider the treatment in this case to be in entirely different territory from the type of medical treatment which is normally being considered. [para 140]

> … the combination here of lifelong and life changing treatment being given to children, with very limited knowledge of the degree to which it will or will not benefit them, is one that gives significant grounds for concern. [para 143]

It seems clear that perceptions of children as young as 10 years of age as medically competent vary by country, state, and the institution where the doctor works, and, by clinicians' beliefs about the long-term benefits of these interventions. We maintain that the claim that kids can consent to extreme life-altering interventions is a fundamentally a philosophical claim (Clark & Virani, 2021). Our view in this matter is that consent is primarily a parental function.

Informed consent should be viewed as a process rather than an event

Most institutions that care for transgender-identified individuals have devised obligatory consent forms that outline the risks and uncertainties of hormonal and surgical gender-affirmative interventions. However, the requisite signatures are frequently collected in a perfunctory manner (Schulz, 2018), akin to signatures collected ahead of a common surgical procedure. The purpose of such informed consent documents appears to be to protect practitioners from lawsuits, rather than attend to the primary ethical foundation of the process.

Although obtaining the signatures is important, the signed document should signify that the process of informed consent has been undertaken over an extended time period and is not simply quickly completed (Vrouenraets et al., 2021). We believe the latter approach poses an ethical concern (Levine, 2019).

The internal dynamics of the trans-identified young person and their families vary considerably. Parental capacities, their private marital and intrafamilial relationships, their cultural awareness, religious and political sensibilities all influence the amount of time necessary to undertake a thorough informed consent process. It is not prudent to suggest a specific duration for the process of informed consent, other than to emphasize that it requires a slow, patient, thoughtful question and answer period as the parents and patient contemplate the meaning of what is known and unknown and whether to embark on alternative approaches to the management of gender dysphoria before the age of full neurological maturity has been reached, mental health comorbidities have been addressed, and a true informed consent by the patient is more likely.

Final thoughts

Sixty years of experience providing medical and surgical assistance to transgender-identified persons have seen many changes in who is treated, when they are treated, and how they are treated. Today, the emphasis has shifted to the treatment of the unprecedented numbers of youth declaring a trans identity. As adolescents pursue social, medical, and surgical interventions, health care providers may experience unease about patients' cognitive and emotional capacities to make decisions with life-changing and enduring consequences. An unrushed informed consent process helps the provider, the parents, and the patient.

Three issues tend to obscure the salience of informed consent: conspicuous mental health problems, uncertainty about the minor's personal capacity to understand the irreversible nature of the interventions, and parental disagreement. Physical and psychiatric comorbidities can contribute to the formation of a new identity, develop as its consequence, or bear no connection to it. Assessing mental health and the minor's functionality is one of the reasons why rapid affirmative care may be dangerous for patients and their families. For example, when situations involve autism, learning disorders, sexual abuse, attachment problems, trauma, separation anxiety, previous depressed or anxious states, neglect, low IQ, past psychotic illness, eating disorders or parental mental illness, clinicians must choose between ignoring these potentially causative conditions and comorbidities and providing appropriate treatment before affirmative care (D'Angelo et al., 2020).

For youth less than the age of majority, informed consent via parents provides a legal route for treatment but it does not make the decisions to transition, provide hormones, or surgically remove breasts or testes less fraught with uncertainty. The best that health professionals can do is to ensure that the consent process informs the patient and parents of the current state of science, which is sorely lacking in quality research. It is the professionals' responsibility to ensure that the benefits patients and parents seek, and the risks they are assuming, are clearly appreciated as they prepare to make this often-excruciating decision.

Young people who have reached the age of majority, but who have not reached full maturation of the brain represent a unique challenge. It is well-recognized that brain remodeling proceeds through the third decade of life, with the prefrontal cortex responsible for executive function and impulse control the last to mature (Katz et al., 2016). The growing number of detransitioners who had been old enough to legally consent to transition, but who no longer felt they were transgender upon reaching their mid-20's, raises additional concerns about this vulnerable age group (Littman, 2021; Vandenbussche, 2021).

When the clinician is uncertain whether a young person is competent to comprehend the implications of the desired treatment—that is, when informed consent cannot inform the patient—the clinician may need more time with the patient. When parents or guardians do

not agree about whether to use puberty blockers or cross-sex hormones, clinicians are in an uneasy spot (Levine, 2021). This occurs in both intact and divorced families. Australia has given legal instructions to clinicians facing these uncertainties: the court is to be asked to decide (Ouliaris, 2021). The court system in the UK has been grappling with similar issues in recent years. While it is a rare case that ends up in a courtroom, clinicians devoted to a deliberate informed consent process are still likely to encounter ethical dilemmas that they cannot resolve.

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Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 14 October 2020. See summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Contents

1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see appendix A). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood (World Health Organisation 2020), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves[1] regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics (Diagnostic and Statistical Manual of Mental Disorders 2013).

GnRH analogues suppress puberty by delaying the development of secondary sexual characteristics. The intention is to alleviate the distress associated with the development of secondary sex characteristics, thereby providing a time for on-going discussion and exploration of gender identity before deciding whether to take less reversible steps. In England, the GnRH analogue triptorelin (a synthetic decapeptide analogue of natural GnRH, which has marketing authorisations for the treatment of prostate cancer, endometriosis and precocious puberty [onset before 8 years in girls and 10 years in boys]) is used for this purpose. The use of triptorelin for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual, and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, support young people and their families in managing the uncertainties inherent in gender identity development and provide on-going opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of GnRH analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex (NHS England 2013).

2. Executive summary of the review

Nine observational studies were included in the evidence review. Five studies were retrospective observational studies (Brik et al. 2020, Joseph et al. 2019, Khatchadourian et al. 2014, Klink et al. 2015, Vlot et al. 2017), 3 studies were prospective longitudinal observational studies (Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016) and 1 study was a cross-sectional study (Staphorsius et al. 2015). Two studies (Costa et al. 2015

[1] Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men (World Health Organisation, Health Topics: Gender).

and Staphorsius et al. 2015) provided comparative evidence and the remaining 7 studies used within-person, before and after comparisons.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]). The mean (±SD) gender dysphoria (UGDS) score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333).

Impact on mental health
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may reduce depression (measured using the Beck Depression Inventory-II [BDI-II]). The mean [±SD] BDI score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004).

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anger (measured using the Trait Anger Scale [TPI]). The mean [±SD] anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503).

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anxiety (measured using the Trait Anxiety Scale [STAI]). The mean [±SD] anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276).

Impact on quality of life
No evidence was identified.

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with health care services, impact on extent of and satisfaction with surgery and stopping treatment. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect body image (measured using the Body Image Scale [BIS]). The mean [±SD] body image (BIS) scores were not statistically significantly different from baseline compared with follow-up for primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145), secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569) or neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620).

Psychosocial impact
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may improve psychosocial impact over time (measured using the Children's Global Assessment Scale [CGAS]). The mean [±SD] CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005).

This study also found that psychosocial functioning may improve over time (measured using the Child Behaviour Checklist [CBCL] and the self-administered Youth Self-Report [YSR]). The mean [±SD] CBCL scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001), internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) and externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). The mean [±SD] YSR scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001), internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) and externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017).

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that during treatment with GnRH analogues psychosocial impact in terms of global functioning may improve over time (measured using the CGAS). In the group receiving GnRH analogues, the mean [±SD] CGAS score was statistically significantly higher (improved) after 6 months (n=60, 64.70 [±13.34]) and 12 months (n=35, 67.40 [±13.39]) compared with baseline (n=101, 58.72 [±11.38], p=0.003 and p<0.001, respectively). However, there was no statistically significant difference in global functioning (CGAS scores) between the group receiving GnRH analogues plus psychological support and the group receiving psychological support only at any time point.

The study by Staphorsius et al. 2015 in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) gave mean [±SD] CBCL scores for each group, but statistical analysis is unclear (transfemales receiving GnRH analogues 57.4 [±9.8], transfemales not receiving GnRH analogues 58.2 [±9.3], transmales receiving GnRH analogues 57.5 [±9.4], transmales not receiving GnRH analogues 63.9 [±10.5]).

Engagement with health care services
The study by Brik et al. 2018 in 143 children and adolescents with gender dysphoria receiving GnRH analogues found that 9 adolescents in the original sampling frame (9/214, 4.2%) were excluded from the study because they stopped attending appointments.

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only had a large loss to follow-up over time. The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.

Impact on extent of and satisfaction with surgery
No evidence was identified.

Stopping treatment
The study by Brik et al. 2018 in 143 children and adolescents with gender dysphoria receiving GnRH analogues reported the reasons for stopping GnRH analogues. During the follow-up period 6.2% (9/143) of adolescents had stopped GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability), although they wanted to continue treatments for gender dysphoria.

The study by Khatchadourian et al. 2014 in 27 adolescents with gender dysphoria who started GnRH analogues reported the reasons for stopping them. Eleven out of 26 where data was available (42%) stopped GnRH analogues during follow up.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Evidence was available for bone density, cognitive development or functioning, and other safety outcomes. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density
The study by Joseph et al. 2019 in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density (measured with the z-score). However, the z-scores were largely within 1 standard deviation of normal,

and actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up:

- The mean z-score [±SD] for lumbar bone mineral apparent density (BMAD) was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [±0.154], 1 year −0.228 [±1.027], p=0.000) and transmales (baseline −0.186 [±1.230], 1 year −0.541 [±1.396], p=0.006).
- The mean z-score [±SD] for lumbar BMAD was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.486 [±0.809], 2 years −0.279 [±0.930], p=0.000) and transmales (baseline −0.361 [±1.439], 2 years −0.913 [±1.318], p=0.001).
- The mean z-score [±SD] for femoral neck bone mineral density (BMD) was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001).

The study by Klink et al. 2015 in 34 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar (transmales only), but not femoral bone density. However, the z-scores are largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from BMD measurements in transmales):

- The mean z-score [±SD] for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (GnRH analogues 0.28 [±0.90], gender-affirming hormones −0.50 [±0.81], p=0.004).

The study by Vlot et al. 2017 in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density. However, the z-scores were largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from in transmales with a bone age ≥14 years). This study reported change in bone density from starting GnRH analogues to starting gender-affirming hormones by bone age:

- The median z-score [range] for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.20 [−1.82 to 1.18], gender-affirming hormones −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years.
- The median z-score [range] for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.05 [−0.78 to 2.94], gender-affirming hormones −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogues 0.27 [−1.60 to 1.80], gender-affirming hormones −0.29 [−2.28 to 0.90], p≤0.0001).

- The median z-score [range] for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.71 [−3.35 to 0.37], gender-affirming hormones −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogues −0.44 [−1.37 to 0.93], gender-affirming hormones −0.36 [−1.50 to 0.46]).
- The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogues 0.27 [−1.39 to 1.32], gender-affirming hormones −0.27 [−1.91 to 1.29], p=0.002).

Cognitive development or functioning

The study by Staphorsius et al. 2015 in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) measured cognitive development or functioning (using an IQ test, and reaction time and accuracy measured using the Tower of London task):

- The mean (±SD) IQ in transfemales receiving GnRH analogues was 94.0 (±10.3) and 109.4 (±21.2) in the control group. In transmales receiving GnRH analogues the mean (±SD) IQ was 95.8 (±15.6) and 98.5 (±15.9) in the control group.
- The mean (±SD) reaction time in transfemales receiving GnRH analogues was 10.9 (±4.1) and 9.9 (±3.1) in the control group. In transmales receiving GnRH analogue it was 9.9 (±3.1) and 10.0 (±2.0) in the control group.
- The mean (±SD) accuracy score in transfemales receiving GnRH analogues was 73.9 (±9.1) and 83.4 (±9.5) in the control group. In transmales receiving GnRH analogues it was 85.7 (±10.5) and 88.8 (±9.7) in the control group.

No statistical analyses or interpretation of the results was reported.

Other safety outcomes

The study by Schagen et al. 2016 in 116 adolescents with gender dysphoria found that GnRH analogues do not affect renal or liver function:

- There was no statistically significant difference between baseline and 1 year results for serum creatinine in transfemales, but there was a statistically significant decrease between baseline and 1 year in transmales (p=0.01).
- Glutamyl transferase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels did not significantly change from baseline to 12 months of treatment.

The study by Khatchadourian et al. 2014 in 27 adolescents with gender dysphoria who started GnRH analogues narratively reported adverse effects from GnRH analogues in 26 adolescents:

- 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated
- 1 transmale developed leg pains and headaches, which eventually resolved
- 1 participant gained 19 kg within 9 months of starting GnRH analogues.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for GnRH analogues in children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria: sex assigned at birth males (transfemales) and sex assigned at birth females (transmales). This included some direct comparisons of these subgroups, and differences were largely seen at baseline as well as follow up. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)
Impact on gender dysphoria
The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females. Sex assigned at birth males had a statistically significantly lower (improved) mean [±SD] UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001), but it was not reported if this was at baseline or follow-up.

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females at baseline and follow up. The mean [±SD] UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean UGDS score: 47.95 [±9.70] versus 56.57 [±3.89]) and follow up (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001).

Impact on mental health
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males compared with sex assigned at birth females. Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression, but sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at baseline and follow up.

- The mean [±SD] depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and follow-up (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057

- The mean [±SD] anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean TPI score [±SD]: 5.22 [±2.76] versus 6.43 [±2.78]) and follow-up (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022
- The mean [±SD] anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and follow-up (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001.

Impact on body image

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that the impact on body image may be different in sex assigned at birth males compared with sex assigned at birth females. Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

- The mean [±SD] BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and follow up (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]) between sex difference p=0.047.
- The mean [±SD] BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and follow up (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001.
- The mean [±SD] BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, 2.60 [±0.58] versus 2.24 [±0.62], between sex difference p=0.777).

Psychosocial impact

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that sex assigned at birth males had statistically significant lower mean [±SD] CGAS scores at baseline compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03), but no conclusions could be drawn.

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth males compared with sex assigned at birth females, but no conclusions could be drawn.

- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females (at baseline or follow up) for the CBCL Total T

score, the CBCL internalising T score, the YSR Total T score or the YSR internalising T score.

- Sex assigned at birth males had statistically higher mean [±SD] CGAS scores compared with sex assigned at birth females at baseline (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and follow up (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021.
- Sex assigned at birth males had statistically lower mean [±SD] CBCL externalising T scores compared with sex assigned at birth females at baseline (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and follow up (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015.
- Sex assigned at birth males had statistically lower mean [±SD] YSR externalising T scores compared with sex assigned at birth females at both baseline (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and follow up (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004.

Bone density

The studies by Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in sex assigned at birth males (see above for details).

Cognitive development or functioning

The study by Staphorsius et al. 2015 provided evidence on cognitive development or functioning in sex assigned at birth males (see above for details).

Other safety outcomes

The study by Schagen et al. 2016 provided evidence on renal function in sex assigned at birth males (see above).

Sex assigned at birth females (transmales)

Impact on gender dysphoria

The studies by de Vries et al. 2011 and Costa et al. 2015 found that gender dysphoria (measured using the UGDS) in sex assigned at birth females is higher than in sex assigned at birth males at baseline and follow up (see above for details).

Impact on mental health

The study by de Vries et al. 2011 found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females compared with sex assigned at birth males. Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression, but sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at both baseline and follow up (see above for details).

Impact on body image

The study by de Vries et al. 2011 found that the impact on body image may be different in sex assigned at birth females compared with sex assigned at birth males. Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different (see above for details).

Psychosocial impact
The studies by de Vries et al. 2011 and Costa et al. 2015 found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth females compared with sex assigned at birth males, but no conclusions could be drawn (see above for details).

Bone density
The studies by Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in sex assigned at birth females (see above for details).

Cognitive development or functioning
The study by Staphorsius et al. 2015 provided evidence on cognitive development or functioning in sex assigned at birth females (see above for details).

Other safety outcomes
The study by Schagen et al. 2016 provided evidence on renal function in sex assigned at birth females (see above for details).

From the evidence selected:

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with GnRH analogues?

(c) what was the duration of treatment with GnRH analogues?

All studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria that was in use at the time. In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-fourth edition, text revision (IV-TR) criteria were used. The study by Brik et al. 2020 used DSM-V criteria. It was not reported how gender dysphoria was defined in the remaining 3 studies.

The studies show variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.

Most studies did not report the duration of treatment with GnRH analogues (Joseph et al. 2019, Khatchadourian et al. 2014, Vlot et al. 2017, Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016), but where this was reported (Brik et al. 2020, Klink et al. 2015, Staphorsius et al. 2015) there was a wide variation ranging from a few months to about 5 years.

Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly. All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

Many of the studies did not report statistical significance or confidence intervals. Changes in outcome scores for clinical effectiveness and bone density were assessed with regards to statistical significance. However, there is relatively little interpretation of whether the changes in outcomes are clinically meaningful.

In the observational, retrospective studies providing evidence on bone density, participants acted as their own controls and change in bone density was determined between starting GnRH analogues and follow up. Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time.

Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. The study by de Vries et al. 2011 reported statistically significant reductions in the Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) scores from baseline to follow up, which include measures of distress. As the aim of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics, this may be an important finding. However, as the studies all lack appropriate controls who were not receiving GnRH analogues, any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the expected increase in bone density (which is expected during puberty). However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after they are stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   b) what were the ages at which participants commenced treatment with GnRH analogues?
   c) what was the duration of treatment with GnRH analogues?

See appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 23 July 2020.

See appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially

relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See appendix C for evidence selection details and appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See appendix G for GRADE Profiles.

4. Summary of included studies

Nine observational studies were identified for inclusion. Five studies were retrospective observational studies (Brik et al. 2020, Joseph et al. 2019, Khatchadourian et al. 2014, Klink et al. 2015, Vlot et al. 2017), 3 studies were prospective longitudinal observational studies (Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016) and 1 study was a cross-sectional study (Staphorsius et al. 2015).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Brik et al. 2020 Retrospective observational single-centre study Netherlands	The study was conducted at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands and involved adolescents with gender dysphoria. The sample size was 143 adolescents (median age at start of treatment was 15.0 years, range 11.1 to 18.6 years in transfemales; 16.1 years, range 10.1 to 17.9 years in transmales) from a sampling frame of 269 children and adolescents registered at the clinic between November 2010 and January 2018.	**Intervention** 143 children and adolescents receiving GnRH analogues (no specific treatment, dose, route or frequency of administration reported). The median duration was 2.1 years (range 1.6–2.8 years). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Stopping treatment

Study	Population	Intervention and comparison	Outcomes reported
	Participants were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, were prepubertal and within the appropriate age range, and had started GnRH analogues. No concomitant treatments were reported.		
Costa et al. 2015 Prospective longitudinal observational single centre cohort study United Kingdom	The study was conducted at the Gender Identity Development Service in London and involved adolescents with gender dysphoria. The sample size was 201 adolescents (mean [±SD] age 15.52±1.41 years, range 12 to 17 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean [±SD] age at the start of GnRH analogues was 16.48 [±1.26] years, range 13 to 17 years. Participants were invited to participate following a 6-month diagnostic process using DSM-IV-TR criteria. No concomitant treatments were reported.	**Intervention** 101 adolescents assessed as being immediately eligible for GnRH analogues (no specific treatment, dose or route of administration reported) plus psychological support. The average duration of treatment was approximately 12 months (no exact figure given). **Comparison** 100 adolescents assessed as not immediately eligible for GnRH analogues (more time needed to make the decision to start GnRH analogues) who had psychological support only. None received GnRH analogues throughout the study.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Psychosocial impact
de Vries et al. 2011 Prospective longitudinal observational single centre before and after study Netherlands	The study was conducted at the Amsterdam gender identity clinic of the VU University Medical Centre and involved adolescents who were defined as “transsexual”. The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Participants were invited to participate if they subsequently started gender-affirming hormones between 2003 and 2009. No diagnostic criteria or concomitant treatments were reported.	**Intervention** 70 individuals assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** No comparator.	**Critical Outcomes** • Gender dysphoria • Mental health (depression, anger and anxiety) **Important outcomes** • Body image • Psychosocial impact

Study	Population	Intervention and comparison	Outcomes reported
Joseph et al. 2019 Retrospective longitudinal observational single centre study United Kingdom	This study was conducted at the Early intervention clinic at University College London Hospital (all participants had been seen at the Gender Identity Development Service in London) and involved adolescents with gender dysphoria. The sample size was 70 adolescents with gender dysphoria (no diagnostic criteria described) all offered GnRH analogues. The mean age at the start of treatment was 13.2 years (SD ±1.4) for transfemales and 12.6 years (SD ±1.0) for transmales. Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported. No concomitant treatments were reported.	**Intervention** GnRH analogues. No specific treatment, duration, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: bone density
Khatchadourian et al. 2014 Retrospective observational chart review single centre study Canada	This study was conducted at the Endocrinology and Diabetes Unit at British Columbia Children's Hospital, Canada and involved youths with gender dysphoria. The sample size was 27 young people with gender dysphoria who started GnRH analogues (at mean age 14.7 [SD ±1.9] years) out of 84 young people seen at the unit between 1998 and 2011. Diagnostic criteria and concomitant treatments were not reported.	**Intervention** 84 young people with gender dysphoria. For GnRH analogues no specific treatment, duration, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Stopping treatment • Safety: adverse effects
Klink et al. 2015 Retrospective longitudinal observational single centre study Netherlands	This study was conducted in the Netherlands at a tertiary referral centre. It is unclear which centre this was. The sample size was 34 adolescents (mean age 14.9 [SD ±1.9] years for transfemales and 15.0 [SD ±2.0] years for transmales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	**Intervention** The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones with discontinuation of GnRH analogues after gonadectomy. Duration of GnRH analogues was 1.3 years (range 0.5 to 3.8 years) in transfemales and 1.5 years (0.25 to 5.2 years in transmales. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: bone density

Study	Population	Intervention and comparison	Outcomes reported
Schagen et al. 2016 Prospective longitudinal study Netherlands	This study was conducted at the Centre of Expertise on Gender Dysphoria at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 116 adolescents (median age [range] 13.6 years [11.6 to 17.9] in transfemales and 14.2 years [11.1 to 18.6] in transmales during first year of GnRH analogues) out of 128 adolescents who started GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	**Intervention** The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg at 0, 2 and 4 weeks followed by intramuscular injections every 4 weeks, for at least 3 months). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: liver and renal function.
Staphorsius et al. 2015 Cross-sectional (single time point) assessment single centre study Netherlands	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 85, of whom 40 were adolescents with gender dysphoria (20 of whom were being treated with GnRH analogues) and 45 were controls without gender dysphoria (not further reported here). Mean (±SD) age 15.1 (±2.4) years in transfemales and 15.8 (±1.9) years in transmales. Details of the sampling frame are not reported. Participants were included if they were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. No concomitant treatments were reported.	**Intervention** The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously or intramuscularly). The mean duration of treatment was 1.6 years (SD ±1.0). **Comparison** Adolescents with gender dysphoria not treated with GnRH analogues.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Psychosocial impact • Safety: cognitive functioning
Vlot et al. 2017 Retrospective observational data analysis study	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 70 adolescents (median age [range] 15.1 years [11.7 to 18.6] for	**Intervention** The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes**

Study	Population	Intervention and comparison	Outcomes reported
Netherlands	transmales and 13.5 years [11.5 to 18.3] for transfemales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were receiving GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported.		• Safety: bone density
Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; GnRH, Gonadotrophin releasing hormone; SD, Standard deviation.			

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender dysphoria **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria. The study measured the impact on gender dysphoria at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333) **(VERY LOW)**.

	This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.
Impact on mental health: depression **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. The study provided evidence for depression measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.**
Impact on mental health: anger **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger. The study provided evidence for anger measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.**

Impact on mental health: anxiety **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. Anxiety was measured using the Trait Anxiety Scale of the State-Trait Personality Inventory (STAI). This is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. The study provided evidence for anxiety at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276) (**VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.**
Quality of life	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified.
Important outcomes	
Impact on body image **Certainty of evidence: very low**	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image (de Vries et al. 2011). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study (de Vries et al. 2011) provided evidence for body image measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) body image (BIS) scores for were not statistically significantly different from baseline compared with follow-up for:

	• primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145) • secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569) • neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.**
Psychosocial impact: global functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. One uncontrolled, observational, prospective cohort study (de Vries et al 2011) and one prospective cross-sectional cohort study (Costa et al. 2015) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children's Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning. One study (de Vries et al. 2011) provided evidence for global functioning (CGAS) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005) **(VERY LOW)**. One study (Costa et al. 2015) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points: • at baseline (T0) in both groups, • after 6 months of psychological support in both groups (T1), • after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and • after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3). The mean [±SD] CGAS score was statistically significantly higher (improved) for all adolescents (including those not receiving GnRH analogues) at T1, T2 or T3 compared with baseline (T0).

	For the immediately eligible group (who received GnRH analogues) versus the delayed eligible group (who did not receive GnRH analogues) there were no statistically significant differences in CGAS scores between the 2 groups at baseline T0 (n=201, p=0.23), T1 (n=201, p=0.73), T2 (n=121, p=0.49) or T3 (n=71, p=0.14) time points. For the immediately eligible group (who received GnRH analogues), the mean (±SD) CGAS score was not statistically significantly different at: • T1 compared with T0 • T2 compared with T1 • T3 compared with T2. The mean (±SD) CGAS score was statistically significantly higher (improved) at: • T2 compared with T0 (n=60, 64.70 [±13.34] versus n=101, 58.72 [±11.38], p=0.003) • T3 compared with T0 (n=35, 67.40 [±13.39] versus n=101, 58.72 [±11.38], p<0.001) • T3 compared with T1 (n=35, 67.40 [±13.93] versus n=101, 60.89 [±12.17], p<0.001) **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.**
Psychosocial impact: psychosocial functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study (de Vries et al, 2011) and 1 cross-sectional observational study (Staphorsius et al. 2015) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent's age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range. One study (de Vries et al. 2011) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and

	• shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). At follow up, the mean (±SD) CBCL scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001 • Internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) • Externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). At follow up, the mean (±SD) YSR scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001) • Internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) • Externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017) **(VERY LOW)**. One study (Staphorsius et al. 2015) assessed CBCL in a cohort of adolescents with gender dysphoria (transfemale: n=18, mean [±SD] age 15.1 [±2.4] years and transmale: n=22, mean [±SD] age 15.8 [±1.9] years) either receiving GnRH analogues (transfemale, n=8 and transmale, n=12), or not receiving GnRH analogues (transfemale, n=10 and transmale, n=10). The mean (±SD) CBCL scores for each group were (statistical analysis unclear): • transfemales (total) 57.8 [±9.2] • transfemales receiving GnRH analogues 57.4 [±9.8] • transfemales not receiving GnRH analogues 58.2 [±9.3] • transmales (total) 60.4 [±10.2] • transmales receiving GnRH analogues 57.5 [±9.4] • transmales not receiving GnRH analogues 63.9 [±10.5] **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues psychosocial functioning may improve, with the proportion of adolescents in the clinical range for some CBCL and YSR scores decreasing over time.**
Engagement with health care services **Certainty of evidence: very low**	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. Two uncontrolled observational cohort studies provided evidence relating to loss to follow up, which could be a marker of engagement with health care services (Brik et al. 2018 and Costa et al. 2015).

	In one retrospective study (Brik et al. 2018), 9 adolescents (9/214, 4.2%) who had stopped attending appointments were excluded from the study between November 2010 and July 2019 **(VERY LOW)**. One prospective study (Costa et al. 2015) had evidence for a large loss to follow-up over time. The sample size at baseline (T0) and 6 months (T1) was 201, which dropped by 39.8% to 121 after 12 months (T2) and by 64.7% to 71 at 18 months follow-up (T3). No explanation of the reasons for loss to follow-up are reported **(VERY LOW)**. Due to their design there was no reported loss to follow-up in the other 3 effectiveness studies (de Vries et al 2011; Khatchadourian et al. 2014; Staphorsius et al. 2015). **These studies provide very low certainty evidence about loss to follow up, which could be a marker of engagement with health care services, during treatment with GnRH analogues. Due to the large variation in rates between studies no conclusions could be drawn.**
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.

Stopping treatment
 	
Certainty of evidence: very low
	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents with gender dysphoria.
	
	Two uncontrolled, retrospective, observational cohort studies provided evidence relating to stopping GnRH analogues. One study had complete reporting of the cohort (Brik et al. 2018), the other (Khatchadourian et al. 2014) had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported.
	
	Brik et al. 2018 narratively reported the reasons for stopping GnRH analogues in a cohort of 143 adolescents (38 transfemales and 105 transmales). Median age at the start of GnRH analogues was 15.0 years (range, 11.1–18.6 years) in transfemales and 16.1 years (range, 10.1–17.9 years) in transmales. Of these adolescents, 125 (87%, 36 transfemales, 89 transmales) subsequently started gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRH analogues. At the time of data collection, the median duration of GnRH analogue use was 2.1 years (1.6–2.8).
	
	During the follow-up period 6.3% (9/143) of adolescents had discontinued GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). The percentages and reasons for stopping were:
	• 2.8% (4/143) stopped GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria:
	  ○ 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues
	  ○ 1 transmale had hot flushes, increased migraines, fear of injections, stress at school and unrelated medical issues, and temporarily stopped treatment (after 4 months) and restarted 5 months later.

	○ 1 transmale had mood swings 4 months after starting GnRH analogues. After 2.2 years had unexplained severe nausea and rapid weight loss and discontinued GnRH analogues after 2.4 years ○ 1 transmale stopped GnRH analogues because of inability to regularly collect medication and attend appointments for injections. • 3.5% (5/143) stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons **(VERY LOW)**. Khatchadourian et al. 2014 narratively reported the reasons for stopping GnRH analogues in a cohort of 26 adolescents (15 transmales and 11 transfemales), 42% (11/26) discontinued GnRH analogues during follow-up between 1998 and 2011. Of 15 transmales receiving GnRH analogues, 14 received testosterone during the observation period, of which: • 7 continued GnRH analogues after starting testosterone • 7 stopped GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: ○ 5 stopped after hysterectomy and salpingo-oophorectomy ○ 1 stopped after 2.2 years (transitioned to gender-affirming hormones) ○ 1 stopped after <2 months due to mood and emotional lability **(VERY LOW)**. Of 11 transfemales receiving GnRH analogues, 5 received oestrogen during the observation period, of which: • 4 continued GnRH analogues after starting oestrogen • 1 stopped GnRH analogues when taking oestrogen (no reason reported) **(VERY LOW)**. Of the remaining 6 transfemales taking GnRH analogues: • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before taking oestrogen (the following year delayed due to heavy smoking) • 1 stopped GnRH analogues after 13 months due not to pursuing transition **(VERY LOW)**. **These studies provide very low certainty evidence for the number of adolescents who stop GnRH analogues and the reasons for this.**

Abbreviations: GnRH, gonadotrophin releasing hormone; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement

Safety	
Change in bone density: lumbar **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in lumbar bone density. Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on lumbar BMAD) between starting with a GnRH analogue and at 1 and 2 year intervals (Joseph et al. 2019), and between starting GnRH analogues and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. It was reported as g/cm^3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMAD increase using z-scores. • The z-score for lumbar BMAD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score [±SD]: baseline 0.486 [0.809], 2 years −0.279 [0.930], p=0.000) and transmales (baseline −0.361 [1.439], 2 years −0.913 [1.318], p=0.001) **(VERY LOW)**. • The z-score for lumbar BMAD was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [0.154], 1 year −0.228 [1.027], p=0.000) and transmales (baseline −0.186 [1.230], 1 year −0.541 [1.396], p=0.006) **(VERY LOW)**. • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between baseline and 1 or 2 years in transfemales or transmales **(VERY LOW)**. Two retrospective observational studies (Klink et al. 2015 and Vlot et al. 2017, n=104 in total) provided non-comparative evidence on change in lumbar BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klink et al. 2015 the z-score for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.28 [±0.90], gender-affirming hormone −0.50 [±0.81], p=0.004). Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales **(VERY LOW)**.

	Vlot et al. 2017 reported change from starting GnRH analogues to starting gender-affirming hormones in lumbar BMAD by bone age. • The z-score for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.20 [−1.82 to 1.18], gender-affirming hormone −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years **(VERY LOW)**. • The z-score for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.05 [−0.78 to 2.94], gender-affirming hormone −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.60 to 1.80], gender-affirming hormone −0.29 [−2.28 to 0.90], p≤0.0001) **(VERY LOW)**. • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales with young or old bone age **(VERY LOW)**. Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on lumbar BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMD increase using z-scores. • The z-score for lumbar BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.130 [0.972], 2 years −0.890 [±1.075], p=0.000) and transmales (baseline −0.715 [±1.406], 2 years −2.000 [1.384], p=0.000) **(VERY LOW)**. • The z-score for lumbar BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline −0.016 [±1.106], 1 year −0.461 [±1.121], p=0.003) and transmales (baseline −0.395 [±1.428], 1 year −1.276 [±1.410], p=0.000) **(VERY LOW)**. • With the exception of transmales, where lumbar BMD in kg/m^2 increased between baseline and 1 year (mean [±SD]: baseline 0.694 [±0.149], 1 year 0.718 [±0.124], p=0.006), actual lumbar BMD values were not statistically significantly different between baseline and 1 or 2 years in transfemales or between 0 and 2 years in transmales **(VERY LOW)**. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in lumbar BMD between starting GnRH analogues and starting gender-affirming hormones. • The z-score for lumbar BMD was not statistically significantly different between starting GnRH analogue and starting gender-affirming hormone treatment in transfemales, but was

	statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.17 [±1.18], gender-affirming hormone −0.72 [±0.99], p<0.001) **(VERY LOW)**. • Actual lumbar BMD in g/cm^2 was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (mean [±SD]: GnRH analogues 0.95 [±0.12], gender-affirming hormones 0.91 [±0.10], p=0.006) **(VERY LOW)**. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD).**
Change in bone density: femoral **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in femoral bone density. Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on femoral BMAD) between starting treatment with a GnRH analogue and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales **(VERY LOW)**. • Actual femoral area BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transmales or transfemales **(VERY LOW)**. One retrospective observational study (Vlot et al. 2017, n=70) provided non-comparative evidence on change in femoral neck (hip) BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • The z-score for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.71 [−3.35 to 0.37], gender-affirming hormone −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogue −0.44 [−1.37 to 0.93], gender-affirming hormone −0.36 [−1.50 to 0.46]) **(VERY LOW)**.

	• The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.39 to 1.32], gender-affirming hormone −0.27 [−1.91 to 1.29], p=0.002) **(VERY LOW)**. • Actual femoral neck BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or in transmales with a young bone age, but were statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.33 [0.25 to 0.39), gender-affirming hormone 0.30 [0.23 to 0.41], p≤0.01) **(VERY LOW)**. Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on femoral BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in femoral neck BMD increase using z-scores. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral neck BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001) **(VERY LOW)**. • The z-score for femoral neck BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline 0.157 [±0.905], 1 year −0.340 [±0.816], p=0.002) and transmales (baseline −0.863 [±1.215], 1 year −1.440 [±1.075], p=0.000) **(VERY LOW)**. • Actual femoral neck BMD values in kg/m^2 were not statistically significantly different between baseline and 1 or 2 years in transmales or transfemales **(VERY LOW)**. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower in transmales (z-score mean [±SD]: GnRH analogue 0.36 [±0.88], gender-affirming hormone −0.35 [±0.79], p=0.001) **(VERY LOW)**. • Actual femoral area BMD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but were

	statistically significantly lower in transmales (mean [±SD] GnRH analogue 0.92 [±0.10], gender-affirming hormone 0.88 [±0.09], p=0.005) **(VERY LOW)**. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD), apart from actual femoral area BMD in transmales.**
Cognitive development or functioning **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for cognitive development and puberty suppression may affect cognitive development or functioning. One cross-sectional observational study (Staphorsius et al. 2015, n=70) provided comparative evidence on cognitive development or functioning in adolescents with gender dysphoria on GnRH analogues compared with adolescents with gender dysphoria not on GnRH analogues. Cognitive functioning was measured using an IQ test. Reaction time (in seconds) and accuracy (percentage of correct trials) were measured using the Tower of London (ToL) task. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. No statistical analyses or interpretation of the results in these groups were reported: • IQ in transfemales (mean [±SD] GnRH analogue 94.0 [±10.3], control 109.4 [±21.2]). IQ transmales (GnRH analogue 95.8 [±15.6], control 98.5 [±15.9]. • Reaction time in transfemales (mean [±SD] GnRH analogue 10.9 [±4.1], control: 9.9 [±3.1]). Reaction time transmales (GnRH analogue 9.9 [±3.1], control 10.0 [±2.0]). • Accuracy score in transfemales (GnRH analogue 73.9 [±9.1], control 83.4 [±9.5]. Accuracy score in transmales (GnRH analogue 85.7 [±10.5], control 88.8 [±9.7]. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning. No conclusions could be drawn.**
Other safety outcomes: kidney function **Certainty of evidence: very low**	This is an important outcome because if renal damage (raised serum creatinine is a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on change in serum creatinine between starting GnRH analogues and at 1 year. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • There was no statistically significant difference between baseline and 1 year for serum creatinine in transfemales (mean [±SD] baseline 70 [±12], 1 year 66 [±13], p=0.20). • There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [±8], 1 year 68 [±13], p=0.01).

	This study provides very low certainty evidence that GnRH analogues do not affect renal function.
Other safety outcomes: liver function **Certainty of evidence: very low**	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on elevated liver enzymes between starting GnRH analogues and during use. No comparative values or statistical analyses were reported. • Glutamyl transferase was not elevated at baseline or during use in any person. • Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during use than at baseline. • Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of use. **This study provides very low certainty evidence (with no statistical analysis) that GnRH analogues do not affect liver function.**
Other safety outcomes: adverse effects **Certainty of evidence: very low**	This is an important outcome because if there are adverse effects, GnRH analogues may need to be stopped. One uncontrolled, retrospective, observational cohort study (Khatchadourian et al. 2014) provided evidence relating to adverse effects from GnRH analogues. It had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Khatchadourian et al. 2014 reported adverse effects in a cohort of 26 adolescents (15 transmales and 11 transfemales) receiving GnRH analogues. Of these: • 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale developed leg pains and headaches, which eventually resolved • 1 participant gained 19 kg within 9 months of starting GnRH analogues. **This study provides very low certainty evidence about potential adverse effects of GnRH analogues. No conclusions could be drawn.**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; IQ, intelligence quotient; NS, not significant; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement

Cost-effectiveness	No studies were identified to assess the cost-effectiveness of GnRH analogues for children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. The mean (±SD) UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean UGDS score [±SD]: 47.95 [±9.70] versus 56.57 [±3.89]) and T1 (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001 **(VERY LOW)**. One further prospective observational longitudinal study (Costa et al. 2015) provided evidence for the impact on gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. Sex assigned at birth males had a statistically significantly lower (improved) mean (±SD) UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001). However, it was not reported if this was baseline or follow-up **(VERY LOW)**. **These studies provide very low certainty evidence that in sex assigned at birth males (transfemales), gender dysphoria is lower than in sex assigned at birth females (transmales).** **Impact on mental health** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for the impact on mental health (depression, anger and anxiety) in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. • The mean (±SD) depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and T1 (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057 • The mean (±SD) anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean TPI score [±SD]: 5.22 [±2.76]

versus 6.43 [±2.78]) and T1 (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022
- The mean (±SD) anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and T1 (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001 **(VERY LOW)**.

This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression. However, sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at both baseline and follow up.

Impact on body image
One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth males.
- The mean (±SD) BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and T1 (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]), between sex difference p=0.047
- The mean (±SD) BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and T1 (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001
- The mean (±SD) BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.60 [±0.58] versus 2.24 [±0.62]) and T1 (n=not reported, 2.32 [±0.59] versus 2.61 [±0.50]), between sex difference p=0.777 **(VERY LOW)**.

This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

Psychosocial impact
One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms

	of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth males. • Sex assigned at birth males had statistically higher mean (±SD) CGAS scores compared with sex assigned at birth females at both baseline (T0) (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and T1 (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL Total T score at T0 or T1 (n=54, p=0.110) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL internalising T score at T0 or T1 (n=54, p=0.286) • Sex assigned at birth males had statistically lower mean (±SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and T1 (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR Total T score at T0 or T1 (n=54, p=0.164) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR internalising T score at T0 or T1 (n=54, p=0.825) • Sex assigned at birth males had statistically lower mean (±SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and T1 (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004 **(VERY LOW)**. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth males. • Sex assigned at birth males had statistically significant lower mean (±SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03) **(VERY LOW)**. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically**

	significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales). **Change in bone density: femoral** Three uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on femoral bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth males (transfemales).** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth males (transfemales). No conclusions could be drawn.** **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth males (transfemales).**
Sex assigned at birth females (transmales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) and one prospective observational longitudinal study (Costa et al. 2015) provided evidence for gender dysphoria in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that in sex assigned at birth females (transmales), gender dysphoria is higher than in sex assigned at birth males (transfemales) at both baseline and follow up.**

	Impact on mental health One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on mental health (depression, anger and anxiety) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression. However, sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at baseline and follow up.** **Impact on body image** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.** **Psychosocial impact** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth females. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results.

	These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales). **Change in bone density: femoral** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on femoral bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth females (transmales), apart from actual femoral area.** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth females. See the safety results table above for a full description of the results. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth females (transmales). No conclusions could be drawn.** **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth females (transmales). See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth females (transmales).**
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at which GnRH analogue started	No evidence was identified.
Age at onset of puberty	No evidence was identified.

Tanner stage at which GnRH analogue started	No evidence was identified.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of mental health condition	No evidence was identified.

Abbreviations: BDI-II, Beck Depression Inventory-II; BIS, Body Image Scale; CBCL, Child Behaviour Checklist; CGAS, Children's Global Assessment Scale; SD, standard deviation; STAI, Trait Anxiety Scale of the State-Trait Personality Inventory; TPI, Trait Anger Scale of the State-Trait Personality Inventory; UGDS, Utrecht Gender Dysphoria Scale; YSR, Youth Self-Report

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with GnRH analogues?

(c) what was the duration of treatment with GnRH analogues?

Outcome	Evidence statement
Diagnostic criteria	In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-IV-TR criteria of gender identity disorder was used. The study by Brik et al. 2020 used DSM-V criteria. The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and the way they think of themselves which must have lasted at least 6 months. It was not reported how gender dysphoria was defined in the remaining 3 studies **(VERY LOW)**. **From the evidence selected, all studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the DSM criteria in use at the time the study was conducted.**
Age when GnRH analogues started	8/9 studies reported the age at which participants started GnRH analogues, either as the mean age (with SD) or median age (with the range): **Study** — **Mean age (±SD)** Costa et al. 2015 — 16.5 years (±1.3) de Vries et al. 2011 — 13.6 years (±1.8) Joseph et al. 2019 — 13.2 years (±1.4) in transfemales; 12.6 years (±1.0) in transmales Khatchadourian et al. 2014 — 14.7 years (±1.9)

<table>
<tr><td></td><td>
<table>
<tr><td>Klink et al. 2015</td><td>14.9 years (±1.9) in transfemales
15.0 years (±2.0) in transmales</td></tr>
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<table>
<tr><th>Study</th><th>Median age (range)</th></tr>
<tr><td>Brik et al. 2020</td><td>15.5 years (11.1–18.6) in transfemales
16.1 years (10.1–17.9) in transmales</td></tr>
<tr><td>Schagen et al. 2016</td><td>13.6 years (11.6–17.9) in transfemales
14.2 years (11.1–18.6) in transmales</td></tr>
<tr><td>Vlot et al. 2017</td><td>13.5 years (11.5–18.3) in transfemales
15.1 years (11.7–18.6) in transmales</td></tr>
</table>
Age at the start of GnRH analogues was not reported in Staphorsius et al. 2015, but participants were required to be at least 12 years (VERY LOW).

The evidence included showed wide variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.
</td></tr>
<tr><td>Duration of treatment</td><td>The duration of treatment with GnRH analogues was reported in 3/9 studies. The median duration was:
• 2.1 years (range 1.6–2.8) in Brik et al. 2020.
• 1.3 years (range 0.5–3.8) in transfemales and 1.5 years (range 0.25–5.2) in transmales in Klink et al. 2015.

In Staphorsius et al. 2015, the mean duration was 1.6 years (SD ±1.0).

In de Vries et al. 2011, the mean duration of time between starting GnRH analogues and gender-affirming hormones was 1.88 years (SD ±1.05).

The evidence included showed wide variation in the duration of treatment with GnRH analogues, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.</td></tr>
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Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of GnRH analogues, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as

assessed using modified GRADE. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly. For example, very little data are reported on how many children and adolescents needed additional mental health support, and for what reasons, or whether additional interventions, and what form and duration (for example drug treatment or counselling) that took. This is a possible confounder for the treatment outcomes in the studies because changes in critical and important outcomes may be attributable to external care rather than the psychological support or GnRH analogues used in the studies.

The studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria in use at the time the study was conducted (either DSM-IV-TR or DSM-V). The definition was unclear in the remaining studies. There was wide variation in the ages at which participants started a GnRH analogue, typically ranging from about 11 to 18 years. Similarly, there was a wide variation in the duration of use, but few studies reported this.

Changes in outcome scores for clinical effectiveness were assessed for statistical significance in the 3 studies reporting these outcomes (Costa et al. 2015; de Vries et al. 2011; Staphorsius et al. 2015). However, there is relatively little interpretation of whether the changes in outcome scores seen in these studies are clinically meaningful.

For some outcomes there was no statistically significant difference from before starting GnRH analogues until just before starting gender-affirming hormones. These were the Utrecht Gender Dysphoria Scale (UGDS) (which was assessed in 1 study de Vries et al. 2011), the Trait Anger (TPI) and Trait Anxiety (STAI) Scales (which were assessed in 1 study de Vries et al. 2011), and Body Image Scale (BIS) which was assessed in 1 study (de Vries et al. 2011).

The Beck Depression Inventory (BDI-II) was used in 1 study (de Vries et al. 2011) to assess change in depression from before starting GnRH analogues to just before starting gender-affirming hormones. The result is statistically significant, with the mean (±SD) BDI-II score decreasing from 8.31 (±7.12) at baseline to 4.95 (±6.27) at follow up (p=0.004). However, both scores fall into the minimal range using the general guidelines for interpretation of BDI-II (0 to 13 minimal, 14 to 19 mild depression, 20 to 28 moderate depression and 29 to 63 severe depression), suggesting that while statistically significant, it is unclear if this is a clinically meaningful change.

Psychosocial outcomes were assessed in 3 studies (Costa et al. 2015; de Vries et al. 2011; Staphorsius et al. 2015) using the Children's Global Assessment Scale (CGAS) and Child Behavior Checklist/Youth Self-Report (CBCL/YSR). The CGAS score was assessed in 2 studies (Costa et al. 2015; de Vries et al. 2011). In de Vries et al. 2011 the mean (±SD) CGAS score statistically significantly increased over time from 70.24 [±10.12] at baseline to 73.90 [±9.63] at follow up. CGAS scores are clinically categorised into 10 categories (10 to 1, 20 to 11 and so on until 100 to 91) and both scores reported were in a single category (71 to 80, no more than slight impairment) suggesting that while statistically significant, it is unclear if this is a clinically meaningful change. The Costa et al. 2015 study does highlight a larger change in CGAS scores from baseline to follow-up (mean [±SD] 58.72 [±11.38] compared with 67.40 [±13.39]), but whether this is clinically meaningful is unclear. The average score moved from the clinical category of 60 to 51 (variable functioning with sporadic difficulties) at baseline to 70 to 61 (some difficulty in a single area, but generally

functioning pretty well) at follow up, but the large standard deviations suggest clinically significant overlaps between the scores from baseline to follow-up.

Psychosocial functioning using the CBCL/YSR was assessed in 2 studies (de Vries et al. 2011; Staphorsius et al. 2015). In de Vries et al. 2011 there was a statistically significant reduction in both CBCL and YSR scores from before starting GnRH analogues to just before starting gender-affirming hormones. The study interpreted the CBCL/YSR with a proportion of adolescents who scored in the clinical range (a T-score above 63), which allows changes in clinically meaningful scores to be assessed, and proportions of adolescents in the clinical range for some CBCL and YSR scores decreased over time. One cross-sectional study (Staphorsius et al. 2015) assessed CBCL scores only, but it was unclear if this was the Total T score, or whether subscales of internalising or externalising scores were also assessed, and whether the results were statistically significant.

The 2 prospective observational studies (Costa et al. 2015; de Vries et al. 2011) are confounded by a number of common factors. Firstly, the single assessment of scores at baseline means it is unclear if scores were stable, already improving or declining before starting treatment. Secondly, in an uncontrolled study any changes in scores from baseline to follow-up could be attributed to a regression-to-mean, for example getting older has been positively associated with maturity and wellbeing. The studies use mean and standard deviations in the descriptive statistics and analyses; however, they do not report testing the normality of data which would support the use of parametric measures. The study by de Vries et al. 2011 used general linear models (regression) to examine between and within group variances (changes in outcomes). In using such models, the data is assumed to be balanced (measured at regular intervals and without missing data), but the large ranges in ages at which participants were assessed and started on various interventions suggests that ascertainment of outcome was unlikely to be regular and missing data was likely. Missing data was handled through listwise deletion (omits those cases with the missing data and analyses the remaining data) which is acceptable if data loss is completely random but for some outcomes where there was incomplete data for individual items this was not random (items were introduced by the authors after the first eligible adolescents had started GnRH analogues). The study provided no detail on whether these assumptions for the modeling were met, they also provided no adequate assessment of whether any regression diagnostics (analysis that seek to assess the validity of a model) or model fit (how much of the variance in outcome is explained by the between and within group variance) were undertaken.

The 2 retrospective observational studies (Brik et al. 2020; Khatchadourian et al. 2014) both only report absolute numbers for each trajectory along with reasons for stopping GnRH analogues. It is difficult to assess outcomes from such single centre studies because there is little comparative data for outcomes from other such services. A lack of any critical or other important outcomes also means the success of the treatment across all the participants is difficult to judge.

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (Joseph et al. 2019; Klink et al. 2015; Vlot et al. 2017). In all 3 studies, the participants acted as their own controls and change in bone density was determined between starting GnRH analogues and either after 1 and 2 year follow-up timepoints (Joseph et al. 2019) or when gender-affirming hormones were started

(Klink et al. 2015 and Vlot et al. 2017). Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is unclear whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

The first study (Brik et al. 2020) was an uncontrolled, retrospective, observational study that assessed the outcome trajectories of adolescents receiving GnRH analogues for gender dysphoria. This study followed-up 143 individuals who had received GnRH analogues (38 transfemales and 105 transmales) using clinical records to show outcomes for up to 9 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods and results are well reported, but no analysis of data was undertaken. The views of adolescents and their parents are particularly difficult to interpret because no data on how many responded to each question and in what ways are reported.

The second study (Costa et al. 2015) was an uncontrolled, prospective observational study which assessed global functioning in adolescents with gender dysphoria using CGAS every 6 months, including during the first 6 months where statistically significant improvements were seen without GnRH analogues. The study is confounded by significant unexplained loss to follow-up (64.7%: from n=201 adolescents to n=71 after 18 months). Missing data for those lost to follow-up maybe more than sufficient to change the direction of effects seen in the study if the reasons for loss to follow-up are systematic (such as deriving little or no benefit from treatment). The study uses clustered data in its analysis, a single outcome (CGAS) measured in clusters (at different visits), and the analysis does not take account of the correlation of scores (data at different time points are not independent) as a significant change in scores early in the study means the successive changes measured against baseline were also significant. The study relies on multiple (>20) pairwise independent *t*-tests to examine change in CGAS between the 4 time points, increasing the possibility of type-I error (a false positive which occurs when a researcher incorrectly rejects a true null hypothesis) because the more tests performed the more likely a statistically significant result will be observed by chance alone.

The Costa et al. 2015 study compares immediately eligible and delayed eligible cohorts, however, it is highly likely that they are non-comparable groups because the immediately eligible group were those able to start GnRH analogues straight away whilst those in the delayed eligible group were either not ready to make a decision about starting treatment (no age comparison was made between the 2 groups so it is unclear if they were a younger cohort than the immediately eligible group) or had comorbid mental health or psychological difficulties. The authors report that those with concomitant problems (such as mental health

problems, substantial problems with peers, or conflicts with parents or siblings) were referred to local mental health services but no details are provided.

The third study (de Vries et al. 2011) was an uncontrolled, prospective observational study which assessed gender dysphoria and psychological functioning before and after puberty suppression in adolescents with gender dysphoria. Although the study mentions the DSM-IV-TR there is no explicit discussion of this, or any other criteria, being used as the diagnostic criteria for study entry. There are no details reported for how the outcomes in the study were assessed, and by whom. The length of follow-up for the outcomes in the model are questionable in relation to whether there was sufficient time for GnRH analogues to have a measurable effect. The time points used are start of GnRH analogues and start of gender-affirming hormones. Overall, the mean time between starting GnRH analogues and gender-affirming hormones was 1.88 (±1.05) years, but the range is as low as just 5 months between the 2 time points, which may be insufficient for any difference in outcome to have occurred in some individuals.

The fourth study (Joseph et al. 2019) was a retrospective, longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria in the UK. For inclusion in the study, participants had to have been assessed by the Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. No other diagnostic criteria, such as the DSM-IV-TR, are discussed. Bone density was assessed using dual energy X-ray absorptiometry (DAXA) scan of the lumbar spine (L1-L4) and the femoral neck at baseline (n=70), 1 year (n=70) and 2 years after starting GnRH analogues (n=39). The results suggest a possible association between GnRH analogues and bone mineral apparent density. However, the evidence is of poor quality, and the results could be due to bias or chance. No concomitant treatments or comorbidities were reported.

The fifth study (Khatchadourian et al. 2014) was an uncontrolled retrospective observational study which describes patient characteristics at presentation, treatment, and response to treatment in 84 adolescents with gender dysphoria, of whom 27 received GnRH analogues. The study used clinical records to show outcomes for up to 13 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods are well reported but the results for those taking GnRH analogues are poorly and incompletely reported, particularly for transfemales, and no analysis of data was undertaken. It is difficult to assess the results for stopping GnRH analogues due to incomplete reporting of this outcome.

The sixth study (Klink et al. 2015) was a retrospective longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria, diagnosed with the DSM-IV-TR criteria. Bone density was assessed when starting GnRH analogues and then when starting gender-affirming hormones. Results are reported for transmales and transfemales separately and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were

reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

The seventh study (Schagen et al. 2016) was a prospective observational study of 116 adolescents which provided very low certainty non-comparative evidence on change in serum creatinine between starting GnRH analogues and 1 year, and liver function during treatment. Statistical analyses were reported for changes in serum creatinine but not for liver function. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time, or concomitant treatments.

The eighth study (Staphorsius et al. 2015) was a cross-sectional study of 85 adolescents, 40 with gender dysphoria (of whom 20 were receiving GnRH analogues) and 45 matched controls (not further reported in this evidence review). The study includes 1 outcome of interest for clinical effectiveness (CBCL) and 1 outcome of interest for safety (cognitive development or functioning). The mean (±SD) CBCL, IQ test, reaction time and accuracy scores were given for each group, but the statistical analysis is unclear. It is not reported what analysis was used or which of the groups were compared, therefore it is difficult to interpret the results.

The ninth study (Vlot et al. 2017) was a retrospective observational study which assessed bone mineral apparent density in adolescents with DSM-IV-TR gender dysphoria. Measurements were taken at the start of GnRH analogues and at the start of gender-affirming hormones. Results are reported for young bone age and old bone age in transmales and transfemales separately, and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

7. Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning) in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. One study reported statistically significant reductions in the Child Behaviour Checklist/Youth Self-Report (CBCL/YSR) scores from

baseline to follow up, and given that the purpose of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics and the CBCL/YSR in part measures distress, this could be an important finding. However, as the studies all lack reasonable controls not receiving GnRH analogues, the natural history of the outcomes measured in the studies is not known and any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the increase in bone density which is expected during puberty. However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after treatment is stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

Appendix A PICO document

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   b) what were the ages at which participants commenced treatment with GnRH analogues?
   c) what was the duration of treatment with GnRH analogues?

PICO table

P – Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by study: The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered: • Sex assigned at birth males. • Sex assigned at birth females. • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months. • The age of onset of gender dysphoria. • The age at which treatment was initiated. • The age of onset of puberty. • Tanner stage at which treatment was initiated. • Children and adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Children and adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), suicide attempts, psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Any GnRH analogue including: triptorelin*; buserelin; histrelin; goserelin (Zoladex); leuprorelin/leuprolide (Prostap); nafarelin.

	* Triptorelin (brand names Gonapeptyl and Decapeptyl) are used in Leeds Hospital, England. The search should include brand names as well as generic names.
C – Comparator(s)	One or a combination of: • Psychological support. • Social transitioning to the gender with which the individual identifies. • No intervention.
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with GnRH analogues was initiated. • The length of treatment with GnRH analogues where possible. **A: Clinical Effectiveness** *Critical to decision making* • **Impact on Gender Dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measures. • **Impact on Quality of Life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measure. *Important to decision making* • **Impact on body Image** This outcome is important because some transgender young people may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. The Body Image Scale could be used as a measure. Other measures

	as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial Impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery – Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may proceed to transitioning surgery. Stated measures of the extent of transitioning surgery and satisfaction with surgery in studies may be reported. • **Stopping treatment** The proportion of patients who stop treatment with GnRH analogues and the reasons why. This outcome is important to patients because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents being treated for gender dysphoria. **B: Safety** • Short and long-term safety and adverse effects of taking GnRH analogues are important because GnRH analogues are not licensed for the treatment of adolescents and children with gender dysphoria. Aspects to be reported on should include: o Impact of the drug use such as its impact on bone density, arterial hypertension, cognitive development/functioning o Impact of withdrawing the drug such as, slipped upper femoral epiphysis, reversibility on the reproductive system, and any others as reported. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.

Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 23 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts and letters were excluded.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 144
Search strategy:

1 Gender Dysphoria/ (485)
2 Gender Identity/ (18452)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3143)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (836)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7435)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12678)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102343)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6974)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114841)
13 or/1-12 (252702)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137479)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852400)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1913257)

17 Minors/ (2574)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2361686)
19 exp pediatrics/ (58118)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (836269)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2024207)
22 Puberty/ (13278)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424246)
24 Schools/ (38104)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468992)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89353)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887838)
29 or/14-28 (5534171)
30 13 and 29 (79263)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79263)
33 Gonadotropin-Releasing Hormone/ (27588)
34 (pubert* adj3 block*).ti,ab. (78)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (17299)
36 (GnRH adj2 analog*).ti,ab. (2541)
37 GnRH*.ti,ab. (20991)
38 "GnRH agonist*".ti,ab. (4040)
39 Triptorelin Pamoate/ (1906)
40 triptorelin.ti,ab. (677)
41 arvekap.ti,ab. (1)
42 ("AY 25650" or AY25650).ti,ab. (1)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (83)
47 diphereline.ti,ab. (17)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (3)
51 triptodur.ti,ab. (1)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (210)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (2119)
58 buserelin.ti,ab. (1304)

59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (69)
61 profact.ti,ab. (2)
62 receptal.ti,ab. (30)
63 suprecur.ti,ab. (4)
64 suprefact.ti,ab. (22)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (55)
67 "LHRH-hydrogel implant".ti,ab. (1)
68 ("RL 0903" or RL0903).ti,ab. (1)
69 ("SPD 424" or SPD424).ti,ab. (1)
70 goserelin.ti,ab. (875)
71 Goserelin/ (1612)
72 ("ici 118630" or ici118630).ti,ab. (51)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (379)
75 leuprorelin.ti,ab. (413)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (23)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (13)
80 Leuprolide/ (2900)
81 leuprolide.ti,ab. (1743)
82 lucrin.ti,ab. (11)
83 lupron.ti,ab. (162)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (3)
86 ("tap 144" or tap144).ti,ab. (40)
87 (a-43818 or a43818).ti,ab. (3)
88 Trenantone.ti,ab. (1)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (6)
91 Nafarelin/ (327)
92 nafarelin.ti,ab. (251)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (12)
98 deslorelin.ti,ab. (263)
99 gonadorelin.ti,ab. (201)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (463)
104 cetrotide.ti,ab. (41)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)

107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (63)
109 gonadoliberin.ti,ab. (143)
110 kryptocur.ti,ab. (6)
111 cetrorelix.ti,ab. (463)
112 cetrotide.ti,ab. (41)
113 antagon.ti,ab. (17)
114 ganirelix.ti,ab. (138)
115 ("ORG 37462" or ORG37462).ti,ab. (3)
116 orgalutran.ti,ab. (20)
117 ("RS 26306" or RS26306).ti,ab. (5)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (11)
120 fertagyl.ti,ab. (11)
121 lutrelef.ti,ab. (5)
122 lutrepulse.ti,ab. (3)
123 relefact.ti,ab. (10)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (6)
126 relisorm.ti,ab. (4)
127 cystorelin.ti,ab. (18)
128 dirigestran.ti,ab. (5)
129 or/33-128 (42216)
130 32 and 129 (416)
131 limit 130 to english language (393)
132 limit 131 to (letter or historical article or comment or editorial or news or case reports) (36)
133 131 not 132 (357)
134 animals/ not humans/ (4686361)
135 133 not 134 (181)
136 limit 135 to yr="2000 -Current" (144)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 21, 2020>
Search date: 23/7/2020
Number of results retrieved:
Search strategy: 42

1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)

8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1645)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2333)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20884)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (968)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15513)
13 or/1-12 (39905)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80723)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (321871)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119783)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (60264)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (69233)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10319)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112800)
29 or/14-28 (525529)
30 13 and 29 (9196)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9197)
33 Gonadotropin-Releasing Hormone/ (0)
34 (pubert* adj3 block*).ti,ab. (19)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1425)
36 (GnRH adj2 analog*).ti,ab. (183)
37 GnRH*.ti,ab. (1695)
38 "GnRH agonist*".ti,ab. (379)
39 Triptorelin Pamoate/ (0)
40 triptorelin.ti,ab. (72)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)

46 Debio.ti,ab. (11)
47 diphereline.ti,ab. (6)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (8)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (59)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (3)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (1)
64 suprefact.ti,ab. (2)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (9)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (68)
71 Goserelin/ (0)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (6)
75 leuprorelin.ti,ab. (47)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (1)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (1)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (121)
82 lucrin.ti,ab. (4)
83 lupron.ti,ab. (10)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (0)
87 (a-43818 or a43818).ti,ab. (0)
88 Trenantone.ti,ab. (1)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (5)
93 ("76932-56-4" or "76932564").ti,ab. (0)

94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (14)
99 gonadorelin.ti,ab. (13)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (31)
104 cetrotide.ti,ab. (5)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (2)
109 gonadoliberin.ti,ab. (4)
110 kryptocur.ti,ab. (1)
111 cetrorelix.ti,ab. (31)
112 cetrotide.ti,ab. (5)
113 antagon.ti,ab. (0)
114 ganirelix.ti,ab. (8)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (3)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (2)
120 fertagyl.ti,ab. (1)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (1)
128 dirigestran.ti,ab. (0)
129 or/33-128 (2332)
130 32 and 129 (45)
131 limit 130 to english language (45)
132 limit 131 to yr="2000 -Current" (42)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 8
Search strategy:

1 Gender Dysphoria/ (0)

2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (486)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (640)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1505)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (178)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2480)
13 or/1-12 (4929)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15496)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53563)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22796)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13087)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12443)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1416)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20166)
29 or/14-28 (88366)
30 13 and 29 (1638)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1638)
33 Gonadotropin-Releasing Hormone/ (0)
34 (pubert* adj3 block*).ti,ab. (2)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (176)
36 (GnRH adj2 analog*).ti,ab. (30)
37 GnRH*.ti,ab. (223)
38 "GnRH agonist*".ti,ab. (49)
39 Triptorelin Pamoate/ (0)

40 triptorelin.ti,ab. (12)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (2)
47 diphereline.ti,ab. (1)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (0)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (7)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (0)
64 suprefact.ti,ab. (1)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (2)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (11)
71 Goserelin/ (0)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (1)
75 leuprorelin.ti,ab. (13)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (1)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (0)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (22)
82 lucrin.ti,ab. (0)
83 lupron.ti,ab. (2)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (1)
87 (a-43818 or a43818).ti,ab. (0)

88 Trenantone.ti,ab. (0)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (4)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (3)
99 gonadorelin.ti,ab. (3)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (6)
104 cetrotide.ti,ab. (2)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (0)
109 gonadoliberin.ti,ab. (0)
110 kryptocur.ti,ab. (0)
111 cetrorelix.ti,ab. (6)
112 cetrotide.ti,ab. (2)
113 antagon.ti,ab. (1)
114 ganirelix.ti,ab. (1)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (0)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (0)
120 fertagyl.ti,ab. (0)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (0)
128 dirigestran.ti,ab. (0)
129 or/33-128 (310)
130 32 and 129 (8)
131 limit 130 to english language (8)
132 limit 131 to yr="2000 -Current" (8)

Database: Medline daily update
Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 1
Search strategy

1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (24)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Gonadotropin-Releasing Hormone/ (11)

34 (pubert* adj3 block*).ti,ab. (0)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (10)
36 (GnRH adj2 analog*).ti,ab. (2)
37 GnRH*.ti,ab. (14)
38 "GnRH agonist*".ti,ab. (4)
39 Triptorelin Pamoate/ (1)
40 triptorelin.ti,ab. (1)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (1)
47 diphereline.ti,ab. (0)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (0)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (0)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (0)
64 suprefact.ti,ab. (0)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (0)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (1)
71 Goserelin/ (2)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (0)
75 leuprorelin.ti,ab. (0)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (0)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (0)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (0)

82 lucrin.ti,ab. (0)
83 lupron.ti,ab. (0)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (0)
87 (a-43818 or a43818).ti,ab. (0)
88 Trenantone.ti,ab. (0)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (0)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (0)
99 gonadorelin.ti,ab. (0)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (0)
104 cetrotide.ti,ab. (0)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (0)
109 gonadoliberin.ti,ab. (0)
110 kryptocur.ti,ab. (0)
111 cetrorelix.ti,ab. (0)
112 cetrotide.ti,ab. (0)
113 antagon.ti,ab. (0)
114 ganirelix.ti,ab. (0)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (0)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (0)
120 fertagyl.ti,ab. (0)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (0)
128 dirigestran.ti,ab. (0)
129 or/33-128 (23)

130 32 and 129 (1)
131 limit 130 to english language (1)
132 limit 131 to yr="2000 -Current" (1)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23/7/2020
Number of results retrieved: 367
Search strategy:

1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)
6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ or sex transformation/ (3058)
8 (gender* adj3 (dysphori* or affirm* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (13005)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (582812)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3437324)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)

25 or/14-24 (7130881)
26 13 and 25 (182161)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (17)
28 26 or 27 (182161)
29 gonadorelin/ (37580)
30 (pubert* adj3 block*).ti,ab. (142)
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (21450)
32 (GnRH adj2 analog*).ti,ab. (4013)
33 GnRH*.ti,ab. (29862)
34 "GnRH agonist*".ti,ab. (6719)
35 exp gonadorelin agonist/ or gonadorelin derivative/ or gonadorelin acetate/ (23304)
36 Triptorelin/ (5427)
37 triptorelin.ti,ab. (1182)
38 arvekap.ti,ab. (3)
39 ("AY 25650" or AY25650).ti,ab. (1)
40 ("BIM 21003" or BIM21003).ti,ab. (0)
41 ("BN 52014" or BN52014).ti,ab. (0)
42 ("CL 118532" or CL118532).ti,ab. (0)
43 Debio.ti,ab. (185)
44 diphereline.ti,ab. (51)
45 moapar.ti,ab. (0)
46 pamorelin.ti,ab. (0)
47 trelstar.ti,ab. (5)
48 triptodur.ti,ab. (1)
49 ("WY 42422" or WY42422).ti,ab. (0)
50 ("WY 42462" or WY42462).ti,ab. (0)
51 gonapeptyl.ti,ab. (10)
52 decapeptyl.ti,ab. (307)
53 salvacyl.ti,ab. (1)
54 buserelin acetate/ or buserelin/ (5164)
55 buserelin.ti,ab. (1604)
56 bigonist.ti,ab. (1)
57 ("hoe 766" or hoe-766 or hoe766).ti,ab. (89)
58 profact.ti,ab. (4)
59 receptal.ti,ab. (37)
60 suprecur.ti,ab. (8)
61 suprefact.ti,ab. (30)
62 tiloryth.ti,ab. (0)
63 histrelin/ (446)
64 histrelin.ti,ab. (107)
65 "LHRH-hydrogel implant".ti,ab. (1)
66 ("RL 0903" or RL0903).ti,ab. (1)
67 ("SPD 424" or SPD424).ti,ab. (1)
68 goserelin.ti,ab. (1487)
69 Goserelin/ (7128)
70 ("ici 118630" or ici118630).ti,ab. (49)
71 ("ZD-9393" or ZD9393).ti,ab. (0)

72 zoladex.ti,ab. (501)
73 leuprorelin/ (11312)
74 leuprorelin.ti,ab. (727)
75 carcinil.ti,ab. (0)
76 enanton*.ti,ab. (38)
77 ginecrin.ti,ab. (1)
78 leuplin.ti,ab. (26)
79 leuprolide.ti,ab. (2788)
80 lucrin.ti,ab. (47)
81 lupron.ti,ab. (361)
82 provren.ti,ab. (0)
83 procrin.ti,ab. (11)
84 ("tap 144" or tap144).ti,ab. (63)
85 (a-43818 or a43818).ti,ab. (3)
86 Trenantone.ti,ab. (7)
87 staladex.ti,ab. (0)
88 prostap.ti,ab. (11)
89 nafarelin acetate/ or nafarelin/ (1441)
90 nafarelin.ti,ab. (324)
91 ("76932-56-4" or "76932564").ti,ab. (0)
92 ("76932-60-0" or "76932600").ti,ab. (0)
93 ("86220-42-0" or "86220420").ti,ab. (0)
94 ("rs 94991 298" or rs94991298).ti,ab. (0)
95 synarel.ti,ab. (28)
96 deslorelin/ (452)
97 deslorelin.ti,ab. (324)
98 gonadorelin.ti,ab. (338)
99 ("33515-09-2" or "33515092").ti,ab. (0)
100 ("51952-41-1" or "51952411").ti,ab. (0)
101 ("52699-48-6" or "52699486").ti,ab. (0)
102 cetrorelix/ (2278)
103 cetrorelix.ti,ab. (717)
104 cetrotide.ti,ab. (113)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (1)
108 ("SB 75" or SB75).ti,ab. (76)
109 gonadoliberin.ti,ab. (152)
110 kryptocur.ti,ab. (6)
111 cetrorelix.ti,ab. (717)
112 cetrotide.ti,ab. (113)
113 antagon.ti,ab. (32)
114 ganirelix/ (1284)
115 ganirelix.ti,ab. (293)
116 ("ORG 37462" or ORG37462).ti,ab. (4)
117 orgalutran/ (1284)
118 orgalutran.ti,ab. (68)
119 ("RS 26306" or RS26306).ti,ab. (6)

120 ("AY 24031" or AY24031).ti,ab. (0)
121 factrel.ti,ab. (14)
122 fertagyl.ti,ab. (20)
123 lutrelef.ti,ab. (7)
124 lutrepulse.ti,ab. (6)
125 relefact.ti,ab. (10)
126 fertiral.ti,ab. (0)
127 (hoe471 or "hoe 471").ti,ab. (4)
128 relisorm.ti,ab. (6)
129 cystorelin.ti,ab. (26)
130 dirigestran.ti,ab. (5)
131 or/29-130 (80790)
132 28 and 131 (988)
133 limit 132 to english language (940)
134 133 not (letter or editorial).pt. (924)
135 134 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (683)
136 nonhuman/ not (human/ and nonhuman/) (4649157)
137 135 not 136 (506)
138 limit 137 to yr="2000 -Current" (420)
139 elsevier.cr. (25912990)
140 138 and 139 (372)
141 remove duplicates from 140 (367)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR – Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 23/7/2020
Number of results retrieved: CDSR – 1; CENTRAL - 8.

#1 [mh ^"Gender Dysphoria"] 3
#2 [mh ^"gender identity"] 227
#3 [mh ^"sexual and gender disorders"] 2
#4 [mh ^transsexualism] 27
#5 [mh ^"transgender persons"] 36
#6 [mh ^"health services for transgender persons"] 0
#7 [mh "sex reassignment procedures"] 4
#8 (gender* NEAR/3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab 308
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab 929
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab 3915
#11 ((sex or gender*) NEAR/3 (reassign* or chang* or transform* or transition*)):ti,ab 493
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab 489

#13 {or #1-#12} 6142
#14 [mh infant] or [mh ^"infant health"] or [mh ^"infant welfare"] 27769
#15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab 69476
#16 [mh child] or [mh "child behavior"] or [mh ^"child health"] or [mh ^"child welfare"] 42703
#17 [mh ^minors] 8
#18 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab 175826
#19 [mh pediatrics]661
#20 (pediatric* or paediatric* or peadiatric*):ti,ab 30663
#21 [mh ^adolescent] or [mh ^"adolescent behavior"] or [mh ^"adolescent health"] 102154
#22 [mh ^puberty] 295
#23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab 34139
#24 [mh ^schools] 1914
#25 [mh ^"Child Day Care Centers"] or [mh nurseries] or [mh ^"schools, nursery"] 277
#26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab 54723
#27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") NEAR/2 (year or years or age or ages or aged)):ti,ab 6710
#28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") NEAR/2 (year or years or age or ages or aged)):ti,ab 196881
#29 {or #14-#28} 469351
#30 #13 and #29 2146
#31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab 0
#32 #30 or #31 2146
#33 [mh ^"Gonadotropin-Releasing Hormone"] 1311
#34 (pubert* NEAR/3 block*):ti,ab 1
#35 ((gonadotrophin or gonadotropin) and releasing):ti,ab 2095
#36 (GnRH NEAR/2 analog*):ti,ab 493
#37 GnRH*:ti,ab 3764
#38 "GnRH agonist*":ti,ab 1399
#39 [mh ^"Triptorelin Pamoate"] 451
#40 triptorelin:ti,ab 451
#41 arvekap:ti,ab 4
#42 ("AY 25650" or AY25650):ti,ab 0
#43 ("BIM 21003" or BIM21003):ti,ab 0
#44 ("BN 52014" or BN52014):ti,ab 0
#45 ("CL 118532" or CL118532):ti,ab 0
#46 Debio:ti,ab 301
#47 diphereline:ti,ab 25
#48 moapar:ti,ab 0
#49 pamorelin:ti,ab 5
#50 trelstar:ti,ab 3

#51 triptodur:ti,ab 0
#52 ("WY 42422" or WY42422):ti,ab 0
#53 ("WY 42462" or WY42462):ti,ab 0
#54 gonapeptyl:ti,ab 11
#55 decapeptyl:ti,ab 135
#56 salvacyl:ti,ab 0
#57 [mh ^Buserelin] 290
#58 Buserelin:ti,ab 339
#59 bigonist:ti,ab 0
#60 ("hoe 766" or hoe-766 or hoe766):ti,ab 11
#61 profact:ti,ab 1
#62 receptal:ti,ab 4
#63 suprecur:ti,ab 0
#64 suprefact:ti,ab 28
#65 tiloryth:ti,ab 0
#66 histrelin:ti,ab 5
#67 "LHRH-hydrogel implant":ti,ab 0
#68 ("RL 0903" or RL0903):ti,ab 0
#69 ("SPD 424" or SPD424):ti,ab 0
#70 goserelin:ti,ab 761
#71 [mh ^goserelin] 568
#72 ("ici 118630" or ici118630):ti,ab 7
#73 ("ZD-9393" or ZD9393):ti,ab 1
#74 zoladex:ti,ab 318
#75 leuprorelin:ti,ab 248
#76 carcinil:ti,ab 0
#77 enanton*:ti,ab 21
#78 ginecrin:ti,ab 1
#79 leuplin:ti,ab 7
#80 [mh ^Leuprolide] 686
#81 leuprolide:ti,ab 696
#82 lucrin:ti,ab 21
#83 lupron:ti,ab 77
#84 provren:ti,ab 0
#85 procrin:ti,ab 2
#86 ("tap 144" or tap144):ti,ab 24
#87 (a-43818 or a43818):ti,ab 0
#88 Trenantone:ti,ab 3
#89 staladex:ti,ab 0
#90 prostap:ti,ab 9
#91 [mh ^Nafarelin] 77
#92 nafarelin:ti,ab 114
#93 ("76932-56-4" or "76932564"):ti,ab 0
#94 ("76932-60-0" or "76932600"):ti,ab 2
#95 ("86220-42-0" or "86220420"):ti,ab 0
#96 ("rs 94991 298" or rs94991298):ti,ab 0
#97 synarel:ti,ab 10
#98 deslorelin:ti,ab 16

#99 gonadorelin:ti,ab 11
#100 ("33515-09-2" or "33515092"):ti,ab 0
#101 ("51952-41-1" or "51952411"):ti,ab 0
#102 ("52699-48-6" or "52699486"):ti,ab 0
#103 cetrorelix:ti,ab 221
#104 cetrotide:ti,ab 111
#105 ("NS 75A" or NS75A):ti,ab 0
#106 ("NS 75B" or NS75B):ti,ab 0
#107 ("SB 075" or SB075):ti,ab 0
#108 ("SB 75" or SB75):ti,ab 10
#109 gonadoliberin:ti,ab 5
#110 kryptocur:ti,ab 0
#111 cetrorelix:ti,ab 221
#112 cetrotide:ti,ab 111
#113 antagon:ti,ab 12
#114 ganirelix:ti,ab 142
#115 ("ORG 37462" or ORG37462):ti,ab 4
#116 orgalutran:ti,ab 45
#117 ("RS 26306" or RS26306):ti,ab 0
#118 ("AY 24031" or AY24031):ti,ab 0
#119 factrel:ti,ab 1
#120 fertagyl:ti,ab 0
#121 lutrelef:ti,ab 0
#122 lutrepulse:ti,ab 1
#123 relefact:ti,ab 1
#124 fertiral:ti,ab 0
#125 (hoe471 or "hoe 471"):ti,ab 3
#126 relisorm:ti,ab 0
#127 cystorelin:ti,ab 0
#128 dirigestran:ti,ab 0
#129 {or #33-#128} 6844
#130 #32 and #129 27
#131 #130 with Cochrane Library publication date Between Jan 2000 and Jul 2020, in Cochrane Reviews 1
#132 #130 27
#133 "conference":pt or (clinicaltrials or trialsearch):so 492465
#134 #132 not #133 9
#135 #134 with Publication Year from 2000 to 2020, in Trials 8

Database: HTA
Platform: CRD
Version: HTA
Search date: 23/7/2020
Number of results retrieved: 26
Search strategy:

1 MeSH DESCRIPTOR Gender Dysphoria EXPLODE ALL TREES 0
2 MeSH DESCRIPTOR Gender Identity EXPLODE ALL TREES 14

3 MeSH DESCRIPTOR Sexual and Gender Disorders EXPLODE ALL TREES 2

4 MeSH DESCRIPTOR Transsexualism EXPLODE ALL TREES 12
5 MeSH DESCRIPTOR Transgender Persons EXPLODE ALL TREES 3
6 MeSH DESCRIPTOR Health Services for Transgender Persons EXPLODE ALL TREES 0
7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1

8 ((gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*))) 28
9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
11 (((sex or gender*) adj3 (reassign* or chang* or transform* or transition*))) 24
12 (male-to-female or m2f or female-to-male or f2m) 86
13 ((transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*)) 0
14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 262
15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) IN HTA 30

*26 results are from 200 onwards. Downloaded as a set to sift for drug terms rather than continuing with search strategy.

Database: APA PsycInfo
Search date: July 2020 (Week 2)
Search Strategy:
---
1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15471)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99560)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)

14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ or exp elementary school students/ or high school students/ or junior high school students/ or middle school students/ (113053)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1772959)
26 11 and 25 (49612)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)
28 26 or 27 (49613)
29 exp Gonadotropic Hormones/ (4226)
30 (pubert* adj3 block*).ti,ab. (29)
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1060)
32 (GnRH adj2 analog*).ti,ab. (49)
33 GnRH*.ti,ab. (998)
34 "GnRH agonist*".ti,ab. (72)
35 triptorelin.ti,ab. (25)
36 arvekap.ti,ab. (0)
37 ("AY 25650" or AY25650).ti,ab. (0)
38 ("BIM 21003" or BIM21003).ti,ab. (0)
39 ("BN 52014" or BN52014).ti,ab. (0)
40 ("CL 118532" or CL118532).ti,ab. (0)
41 Debio.ti,ab. (7)
42 diphereline.ti,ab. (0)
43 moapar.ti,ab. (0)
44 pamorelin.ti,ab. (0)
45 trelstar.ti,ab. (0)
46 triptodur.ti,ab. (0)
47 ("WY 42422" or WY42422).ti,ab. (0)
48 ("WY 42462" or WY42462).ti,ab. (0)
49 gonapeptyl.ti,ab. (0)
50 decapeptyl.ti,ab. (3)
51 salvacyl.ti,ab. (1)

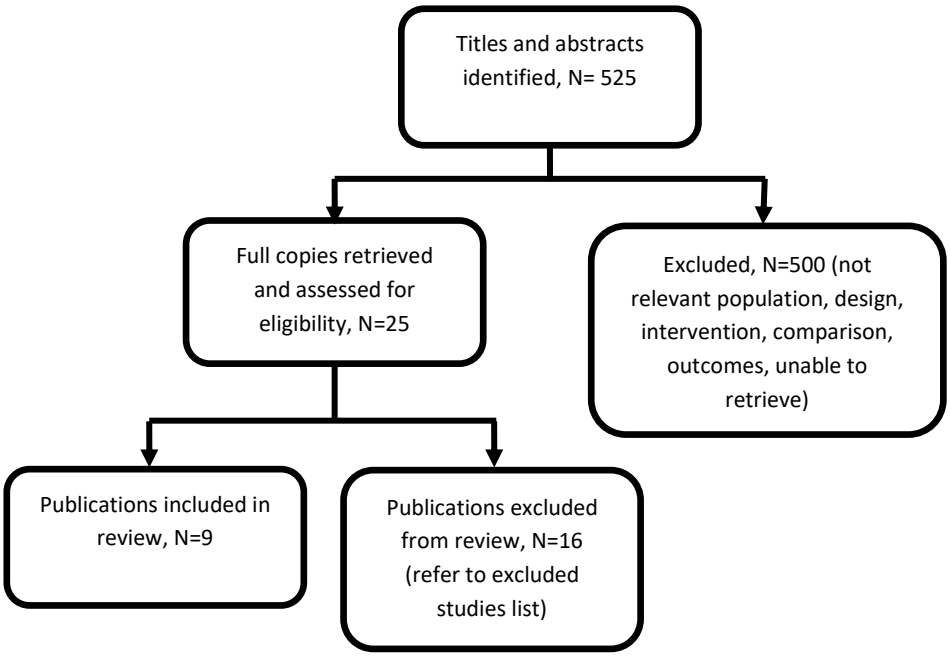
52 buserelin.ti,ab. (6)
53 bigonist.ti,ab. (0)
54 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
55 profact.ti,ab. (0)
56 receptal.ti,ab. (0)
57 suprecur.ti,ab. (0)
58 suprefact.ti,ab. (0)
59 tiloryth.ti,ab. (0)
60 histrelin.ti,ab. (1)
61 "LHRH-hydrogel implant".ti,ab. (0)
62 ("RL 0903" or RL0903).ti,ab. (0)
63 ("SPD 424" or SPD424).ti,ab. (0)
64 goserelin.ti,ab. (30)
65 ("ici 118630" or ici118630).ti,ab. (0)
66 ("ZD-9393" or ZD9393).ti,ab. (0)
67 zoladex.ti,ab. (3)
68 leuprorelin.ti,ab. (12)
69 carcinil.ti,ab. (0)
70 enanton*.ti,ab. (1)
71 ginecrin.ti,ab. (0)
72 leuplin.ti,ab. (0)
73 leuprolide.ti,ab. (79)
74 lucrin.ti,ab. (1)
75 lupron.ti,ab. (18)
76 provren.ti,ab. (0)
77 procrin.ti,ab. (0)
78 ("tap 144" or tap144).ti,ab. (1)
79 (a-43818 or a43818).ti,ab. (0)
80 Trenantone.ti,ab. (0)
81 staladex.ti,ab. (0)
82 prostap.ti,ab. (0)
83 nafarelin.ti,ab. (1)
84 ("76932-56-4" or "76932564").ti,ab. (0)
85 ("76932-60-0" or "76932600").ti,ab. (0)
86 ("86220-42-0" or "86220420").ti,ab. (0)
87 ("rs 94991 298" or rs94991298).ti,ab. (0)
88 synarel.ti,ab. (0)
89 deslorelin.ti,ab. (8)
90 gonadorelin.ti,ab. (3)
91 ("33515-09-2" or "33515092").ti,ab. (0)
92 ("51952-41-1" or "51952411").ti,ab. (0)
93 ("52699-48-6" or "52699486").ti,ab. (0)
94 cetrorelix.ti,ab. (9)
95 cetrotide.ti,ab. (0)
96 ("NS 75A" or NS75A).ti,ab. (0)
97 ("NS 75B" or NS75B).ti,ab. (0)
98 ("SB 075" or SB075).ti,ab. (0)
99 ("SB 75" or SB75).ti,ab. (1)

100 gonadoliberin.ti,ab. (1)
101 kryptocur.ti,ab. (0)
102 cetrorelix.ti,ab. (9)
103 cetrotide.ti,ab. (0)
104 antagon.ti,ab. (0)
105 ganirelix.ti,ab. (0)
106 ("ORG 37462" or ORG37462).ti,ab. (0)
107 orgalutran.ti,ab. (0)
108 ("RS 26306" or RS26306).ti,ab. (0)
109 ("AY 24031" or AY24031).ti,ab. (0)
110 factrel.ti,ab. (0)
111 fertagyl.ti,ab. (0)
112 lutrelef.ti,ab. (0)
113 lutrepulse.ti,ab. (0)
114 relefact.ti,ab. (0)
115 fertiral.ti,ab. (0)
116 (hoe471 or "hoe 471").ti,ab. (0)
117 relisorm.ti,ab. (0)
118 cystorelin.ti,ab. (0)
119 dirigestran.ti,ab. (0)
120 or/29-119 (4869)
121 28 and 120 (130)
122 limit 121 to english language (120)
123 limit 122 to yr="2000 -Current" (93)

Appendix C Evidence selection

The literature searches identified 525 references. These were screened using their titles and abstracts and 25 references were obtained and assessed for relevance. Of these, 9 references are included in the evidence review. The remaining 16 references were excluded and are listed in appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8	Intervention – data for GnRH analogues not reported separately from other interventions
Bechard, Melanie, Vanderlaan, Doug P, Wood, Hayley et al. (2017) Psychosocial and Psychological Vulnerability in Adolescents with Gender Dysphoria: A "Proof of Principle" Study. Journal of sex & marital therapy 43(7): 678-688	Population – no GnRH analogues at time of study
Chew, Denise, Anderson, Jemma, Williams, Katrina et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4)	All primary studies included apart from 1 conference abstract
de Vries, Annelou L C, McGuire, Jenifer K et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696-704	Population – relevant population included in de Vries et al. 2011
Ghelani, Rahul, Lim, Cheryl, Brain, Caroline et al. (2020) Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. Journal of pediatric endocrinology & metabolism: JPEM 33(1): 107-112	Outcomes – not in the PICO

Study reference	Reason for exclusion
Giovanardi, G, Morales, P, Mirabella, M et al. (2019) Transition memories: experiences of trans adult women with hormone therapy and their beliefs on the usage of hormone blockers to suppress puberty. Journal of endocrinological investigation 42(10): 1231-1240	Population – adults only
Hewitt, Jacqueline K, Paul, Campbell, Kasiannan, Porpavai et al. (2012) Hormone treatment of gender identity disorder in a cohort of children and adolescents. The Medical journal of Australia 196(9): 578-81	Outcomes – no data reported for relevant outcomes
Jensen, R.K., Jensen, J.K., Simons, L.K. et al. (2019) Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgender Health 4(1): 300-303	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee, Wiepjes, Chantal M et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The journal of sexual medicine 15(2): 251-260	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3)	Outcomes – not in the PICO
Lopez, Carla Marisa, Solomon, Daniel, Boulware, Susan D et al. (2018) Trends in the use of puberty blockers among transgender children in the United States. Journal of pediatric endocrinology & metabolism : JPEM 31(6): 665-670	Outcomes – not in the PICO
Schagen, Sebastian E E, Lustenhouwer, Paul, Cohen-Kettenis, Peggy T et al. (2018) Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. The journal of sexual medicine 15(9): 1357-1363	Outcomes – not in the PICO
Swendiman, Robert A, Vogiatzi, Maria G, Alter, Craig A et al. (2019) Histrelin implantation in the pediatric population: A 10-year institutional experience. Journal of pediatric surgery 54(7): 1457-1461	Population – less than 10% of participants had gender dysphoria; data not reported separately
Turban, Jack L, King, Dana, Carswell, Jeremi M et al. (2020) Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 145(2)	Intervention – data for GnRH analogues not reported separately from other interventions
Vrouenraets, Lieke Josephina Jeanne Johanna, Fredriks, A Miranda, Hannema, Sabine E et al. (2016) Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. Archives of sexual behavior 45(7): 1697-703	Outcomes – not in the PICO
Zucker, Kenneth J, Bradley, Susan J, Owen-Anderson, Allison et al. (2010) Puberty-blocking hormonal therapy for adolescents with gender identity disorder: A descriptive clinical study. Journal of Gay & Lesbian Mental Health 15(1): 58-82	Intervention – data for GnRH analogues not reported separately from other interventions

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Brik T, Vrouenraets L, de Vries M, et al. (2020) Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Archives of Sexual Behaviour https://doi.org/10.1007/s10508-020-01660-8 Netherlands Retrospective observational single-centre study To document trajectories after the initiation of GnRH analogue and explore reasons for extended use and discontinuation of GnRH analogues. Includes participants seen between November 2010 and January 1, 2018.	Inclusion criteria were adolescents with gender dysphoria, according to the DSM-5 criteria, seen at the single centre and treated with GnRH analogues between November 2010 and January 1, 2018. The study excluded adolescents without a diagnosis of gender dysphoria, those who had coexisting problems that interfered with the diagnostic process and/or might interfere with successful treatment (not further defined), those adolescents not wanting hormones, those with ongoing diagnostic evaluation and those who did not attend appointments. The sample consisted of 143 adolescents meeting the inclusion/exclusion criteria, 38 transfemales, 105 transmales, with median ages of 15.0 years (range 11.1 to 18.6 years) and 16.1 years	The study only reports that GnRH analogues were given, no specific drug, dose, route, or frequency of administration are reported. No comparator cohort was used in the study. Follow-up was at (up to) 9 years (last follow-up July 2019).	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact*** Not assessed. ***Engagement with health care services*** Not formally assessed but the study reported that out of 214 age and developmentally appropriate adolescents for potential inclusion in the study, 9 were excluded as they stopped attending appointments (4.2%). ***Stopping treatment*** Of the 143 adolescents, 9 (6.2%, 1 transfemale and 8 transmales) stopped taking GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Four adolescents (2.8%) discontinued GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: • 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues (later had gender-affirming hormones at an adult gender clinic)[1] • 1 transmale experienced hot flushes, increased migraines, had a fear of injections, stress at school and unrelated medical issues, and	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. no-non exposed cohort 3. secure record 4. yes **Domain 2: Comparability** 1. no comparator **Domain 3: Outcome** 1. record linkage 2. yes 3. complete follow-up **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Source of funding: not reported.

	(range 10.1 to 17.9 years), respectively at commencement of GnRH analogues. Of the 143 adolescents in the study, 125 (87%, 36 transfemales and 89 transmales) subsequently started treatment with gender-affirming hormones after median 1.0 (range 0.5 to 3.8) years and 0.8 (0.3 to 3.7) years, respectively. Median age at the start of gender-affirming hormones was 16.2 years (range 14.5 to 18.6 years) in transfemales and 17.1 years (range 14.9 to 18.8 years) in transmales. Five adolescents who used GnRH analogues had not started gender-affirming hormones at the time of data collection as they were not yet eligible for this treatment due to age. At the time of data collection, they had used GnRH analogues for a median duration of 2.1 years (range 1.6 to 2.8). Tanner stage was not reported. Six adolescents had been referred to a gender clinic elsewhere for further		temporarily discontinued treatment (after 4 months)[2] • 1 transmale experienced mood swings 4 months after commencing GnRH analogues. After 2.2 years he developed unexplained severe nausea and rapid weight loss and due to his general condition discontinued GnRH analogues after 2.4 years[3] • 1 transmale stopped GnRH analogues as his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections[4] Five adolescents (3.5%) stopped treatment as they no longer wished to continue with gender-affirming treatment. • 1 adolescent had been very distressed about breast development at the start of GnRH analogues and later thought that she might want to live as a woman without breasts. She did not want to live as a boy and discontinued GnRH analogues, although dreaded breast development and menstruation. • 1 adolescent experienced concurrent psychosocial problems interfering with the exploration of gender identity and did not currently want treatment.[5] • 1 adolescent felt more in between male and female and therefore did not want to continue with GnRH analogues.[6] • 1 adolescent made a social transition while using GnRH	

	treatment, including 1 who had prolonged use.		analogues and shortly after decided to discontinue treatment.[7] • 1 adolescent discontinued after using GnRH analogues as the treatment allowed them to feel who they were.[8]	

[1] The adolescent later indicated "I was already fully matured when I started GnRH analogues, menstruations were already suppressed by contraceptives. For me, it had no added value" (transmale, age 19 years).
[2] The adolescent restarted endocrine treatment (testosterone) 5 months later.
[3] The adolescent recovered over the next 2 years and subsequently started lynestrenol and testosterone treatment.
[4] The adolescent subsequently started lynestrenol to suppress menses, he was not yet eligible for testosterone treatment.
[5] The adolescent later reflected that "The decision to stop GnRH analogues to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment" (adolescent assigned female sex at birth, age 16 years).
[6] The adolescent stated "At the moment, I feel more like 'I am' instead of 'I am a woman' or 'I am a man'" (adolescent assigned female sex at birth, age 16 years).
[7] The adolescent stated that "he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.
[8] The adolescent stated "After using GnRH analogues for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman" (adolescent assigned female sex at birth, age 18 years).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Costa R, Dunsford M, Skagerberg E, et al. (2015) Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. Journal of Sexual Medicine 12(11):2206-14. United Kingdom Prospective longitudinal observational single centre cohort study Includes participants referred to the service between 2010 and 2014.	Adolescents with gender dysphoria who completed a 6-month diagnostic process using DSM-IV-TR criteria for gender dysphoria (comprising the gender dysphoria assessment and psychological interventions) either immediately eligible for treatment with GnRH analogues or delayed eligible for treatment with GnRH analogues (received psychological support without any physical intervention). No exclusion criteria were reported. The sample consisted of 201 adolescents (sex assigned at birth male to female ratio 1:1.6)	**Intervention** 101 individuals were assessed as being immediately eligible for use of GnRH analogues (no specific treatment, dose or route, or frequency of administration reported but all received psychological support). **Comparison** The analyses were between the immediately eligible	**Critical outcomes** ***Impact on gender dysphoria*** The Utrecht gender dysphoria scale (UGDS) was used to assess adolescents' gender dysphoria related discomfort. The Cronbach's alpha (α) for the study was reported as 0.76 to 0.88, suggesting good internal consistency. UGDS was only reported once, for 160 adolescents (50 sex assigned at birth males and 110 sex assigned at birth females). The assessment time point is not reported (baseline or follow-up) and the comparison for gender related discomfort was between sex assigned at birth males and sex assigned at birth females. Sex assigned at birth males had a mean (±SD) UGDS score of 51.6 [±9.7] versus sex assigned at birth	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. drawn from the same community as the exposed cohort. 3. secure record 4. no **Domain 2: Comparability** 1. partial comparator **Domain 3: Outcome** 1. independent assessment (unclear if blinded) 2. yes 3. incomplete follow-up

	mean (±SD) age 15.52±1.41 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean (±SD) age (n=201) at the start of GnRH analogues was 16.48 [±1.26], range 13 to 17 years. The interval from the start of the diagnostic procedure to the start of puberty suppression took approximately 1.5 years [±0.63] from baseline. None of the delayed eligible individuals received puberty suppression at the time of this study. Tanner stage was not reported.	and delayed eligible (n=100) adolescents, Baseline assessment (following diagnostic procedure) was followed by follow-up at 6 months from baseline (T1), 12 months from baseline (T2) and 18 months from baseline (T3).	females score of 56.1 [±4.3], *t*-test 4.07; p<0.001. ***Impact on mental health*** Not assessed. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Psychosocial impact*** The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS was administered by psychologists, psychotherapists, and psychiatrists (intra-class correlation assessment was 0.76 ≤ Cronbach's α ≤0.94). At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and sex assigned at birth females (all p>0.1). In comparison with sex assigned at birth females, sex assigned at birth males had statistically significantly lower mean (±SD) baseline CGAS scores (55.4 [±12.7] versus 59.2 [11.8]; *t*-test 2.15; p=0.03). There was no statistically significant difference in mean (±SD) CGAS scores at baseline (T0) between immediately eligible adolescents and delayed eligible adolescents (n=201, 58.72 [±11.38] versus 56.63 [±13.14]; *t*-test 1.21; p=0.23). **Immediately eligible compared with delayed eligible participants** At follow-up, there was no statistically significant difference in mean (±SD)	**Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Large unexplained loss to follow-up (64.7%) at T3. Source of funding: not reported.

			CGAS scores at any follow-up time point (T1, T2 or T3) between immediately eligible adolescents and delayed eligible adolescents: • T1, n=201, 60.89 [±12.17] versus 60.29 [±12.81]; *t*-test 0.34; p=0.73 • T2, n=121, 64.70 [±13.34] versus 62.97 [±14.10]; *t*-test 0.69; p=0.49 • T3, n=71, 67.40 [±13.93] versus 62.53 [±13.54]; *t*-test 1.49; p=0.14. **All participants** There was a statistically significant increase in mean (±SD) CGAS scores at any follow-up time point (T1, T2 or T3) compared with baseline (T0) for the all adolescents group: • T0 (n=201) versus T1 (n=201), 57.73 [±12.27] versus 60.68 [±12.47]; *t*-test 4.87; p<0.001 • T0 (n=201) versus T2 (n=121), 57.73 [±12.27] versus 63.31 [±14.41]; *t*-test 3.70; p<0.001 • T0 (n=201) versus T3 (n=71), 57.73 [±12.27] versus 64.93 [±13.85]; *t*-test 4.11; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 but not for the periods T1 to T2 and T2 to T3, for all adolescents: • T1 (n=201) versus T2 (n=121), 60.68 [±12.47] versus 63.31 [±14.41]; *t*-test 1.73; p<0.08 • T1 (n=201) versus T3 (n=71), 60.68 [±12.47] versus 64.93 [±13.85], *t*-test 2.40; p<0.02 • T2 (n=121) versus T3 (n=71), 63.31 [±14.41] versus 64.93 [±13.85], *t*-test 0.76; p=0.45	

			There were no statistically significant differences in CGAS scores between sex assigned at birth males and sex assigned at birth females with gender dysphoria in all the follow-up evaluations (all p>0.1). Delayed eligible and immediately eligible adolescents with gender dysphoria were not statistically significantly different for demographic variables (all p>0.1). **Immediately eligible participants** There was a statistically significant increase in mean (±SD) CGAS scores at follow-up times T2 and T3 compared with baseline (T0) but not for T0 versus T1, for the immediately eligible adolescents: • T0 (n=101) versus T1 (n=101), 58.72 [±11.38] versus 60.89 [±12.17]; *t*-test 1.31; p=0.19 • T0 (n=101) versus T2 (n=60), 58.72 [±11.38] versus 64.70 [±13.34]; *t*-test 3.02; p=0.003 • T0 (n=101) versus T3 (n=35), 58.72 [±11.38] versus 67.40 [±13.93]; *t*-test 3.66; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 with each other but not for the periods T1 to T2 and T2 to T3, for the immediately eligible adolescents: • T1 (n=101) versus T2 (n=60), 60.89 [±12.17] versus 64.70 [±13.34]; *t*-test 1.85; p=0.07 • T1 (n=101) versus T3 (n=35), 60.89 [±12.17] versus 67.40 [±13.93], *t*-test 2.63; p<0.001	

			• T2 (n=60) versus T3 (n=35), 64.70 [±13.34] versus 67.40 [±13.93], *t*-test 0.94; p=0.35 The immediately eligible adolescents had a CGAS score which was not statistically significantly different compared to the sample of children/ adolescents without observed psychological /psychiatric symptoms after 12 months of puberty suppression (T3, *t*=0.01, *p*=0.99).	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
de Vries A, Steensma T, Doreleijers T, et al. (2011) Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. The Journal of Sexual Medicine 8 (8):2276-83. Netherlands Prospective longitudinal observational single centre before and after study.	The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Inclusion criteria were if they subsequently started gender-affirming hormones between 2003 and 2009 (mean [±SD] age at start of GnRH analogues was 14.75 [±1.92] years)[1]. No specific exclusion criteria were described. No diagnostic criteria or concomitant treatments were reported. Tanner stage of the included adolescents was not reported.	**Intervention** 70 adolescents were assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** The same 70 adolescents were assessed again at follow-up (T1), shortly before starting gender-affirming hormones. Not all adolescents completed all assessments for all items[2].	**Critical outcomes** ***Impact on gender dysphoria*** Impact on gender dysphoria was assessed using the Utrecht Gender Dysphoria Scale (UGDS). • There was no statistically significant difference in UGDS scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more gender dysphoria, *F* (*df, errdf*), *P*: 15.98 (1,39), p<0.001. ***Impact on mental health*** Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II). • There was a statistically significant reduction in BDI score between T0 and T1, n=41, 8.31 [±7.12] versus 4.95 [±6.72], *F* (*df, errdf*), *P*: 9.28 (1,39), p=0.004. • There was no statistically significant difference between sex assigned at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. no non-exposed cohort 3. no description 4. no **Domain 2: Comparability** 1. study controls for age, age at start of treatment, IQ, and parental factors **Domain 3: Outcome** 1. no description 2. no/unclear 3. complete **Overall quality is assessed as poor**. Other comments: Physical and psychological comorbidity was not reported, concomitant use of

			birth males and sex assigned at birth females, *F* (*df, errdf*), *P*: 3.85 (1,39), p=0.057. Anger and anxiety were assessed using Trait Anger and Anxiety (TPI and STAI, respectively) Scales of the State-Trait Personality Inventory. • There was no statistically significant difference in anger (TPI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anger compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.70 (1,39), p=0.022. • Similarly, there was no statistically significant difference in anxiety (STAI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anxiety compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 16.07 (1,39), p<0.001. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Impact on body image*** Impact on body image was assessed using the Body Image Scale to measure body satisfaction (BIS).	other medicines was not reported. Source of funding: This study was supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development.

			There was no statistically significant difference between T0 and T1 for any of the 3 BIS scores (primary sex characteristics, secondary sex characteristics or neutral characteristics, n=57). There were statistically significant differences between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more dissatisfaction, for: • primary sexual characteristics, *F* (*df, errdf*), *P*: 4.11 (1,55), p=0.047. • secondary sexual characteristics, *F* (*df, errdf*), *P*: 11.57 (1,55), p=0.001. But no statistically significant difference between sex assigned at birth males and sex assigned at birth females was found for neutral characteristics. However, there was a significant interaction effect between sex assigned at birth sex and the changes of gender dysphoria between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary sex characteristics compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 14.59 (1,55), p<0.001) and neutral characteristics, *F* (*df, errdf*), *P*: 15.26 (1,55), p<0.001). ***Psychosocial impact*** Psychosocial impact was assessed using both the Child Behaviour Checklist (CBCL) and the Youth Self-Report (YSR) to parents and adolescents, respectively. The Children's Global Assessment Scale was also reported. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] parental	

			CBCL scores between T0 and T1[4] for all adolescents (n=54): • Total score (T0 – T1) 60.70 [±12.76] versus 54.46 [±11.23], *F* (*df, errdf*), *P*: 26.17 (1,52), p<0.001. • Internalising score (T0 – T1) 61.00 [±12.21] versus 54.56 [±10.22], *F* (*df, errdf*), *P*: 22.93 (1,52), p<0.001. • Externalising score (T0 – T1) 58.04 [±12.99] versus 53.81 [±11.86], *F* (*df, errdf*), *P*: 12.04 (1,52), p=0.001. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising CBCL score but there was a significant difference for the externalising score: • Externalising score, *F* (*df, errdf*), *P*: 6.29 (1,52), p=0.015. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] YSR scores between T0 and T1 for all adolescents (n=54): • Total score (T0 – T1) 55.46 [±11.56] versus 50.00 [±10.56], *F* (*df, errdf*), *P*: 16.24 (1,52), p<0.001. • Internalising score (T0 – T1) 56.04 [±12.49] versus 49.78 [±11.63], *F* (*df, errdf*), *P*: 15.05 (1,52), p<0.001. • Externalising score (T0 – T1) 53.30 [±11.87] versus 49.98 [±9.35], *F* (*df, errdf*), *P*: 7.26 (1,52), p=0.009. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising YSR score but there was a significant difference for the externalising score:	

			• Externalising score, *F* (*df, errdf*), *P*: 9.14 (1,52), p=0.004. There was a statistically significant increase in CGAS mean (±SD) score between T0 and T1 (n=41), 70.24 [±10.12] versus 73.90 [±9.63], *F* (*df, errdf*), *P*: 8.76 (1,39), p=0.005. There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting lower score for global functioning compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.77 (1,52), p=0.021. The proportion of adolescents scoring in the clinical range significantly decreased between T0 and T1, on the CBCL total problem scale (44.4% versus 22.2%, X^2[1] = 6.00, p=0.001), and the internalising scale (29.6% versus 11.1%, X^2[1] = 5.71, p=0.017) of the YSR.	

[1] There were statistically significant mean age [±SD] differences between sex assigned at birth males and sex assigned at birth females for age at assessment (13.14 [±1.55] versus 14.10 [±1.99] years, p=0.028), age at start of GnRH analogues (14.25 [±1.79] versus 15.21 [±1.95] years, p=0.036) and age at the start of gender-affirming hormones (16.24 [±1.21] versus 16.99 [±1.09] years, p=0.008). No statistically significant differences were seen for other baseline characteristics, time between GnRH analogue and gender-affirming hormones, full scale IQ, parental marital status, education, and sexual attraction to own, other or both sexes.
[2] Independent t-tests between mean scores on the CBCL, YSR, BDI, TPI, STAI, CGAS, UGS, and BIS of adolescents who completed both assessments and mean scores of adolescents who completed only one of the assessments revealed no significant differences on all used measures, at neither T0 or at T1.
[3] The CBCL/YSR has 2 components: Internalising score which sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores; externalising score which sums rule-breaking and aggressive behaviour. The total problems score is the sum of the scores of all the problem items. The YSR is a child self-report version of the CBCL.
[4] A repeated measures ANOVA (analysis of variance) was used.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Joseph T, Ting J, Butler G. (2019) The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. Journal of pediatric endocrinology & metabolism 32(10): 1077-1081	Adolescents (12 to 14 years) with gender dysphoria (no diagnostic criteria described), n=70, including 31 transfemales and 39 transmales.	Treatment with a GnRH analogue for at least 1 year or ongoing until they reached 16 years. No specific treatment, dose or route of	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar[1]*** **Lumbar spine bone mineral apparent density (BMAD)[2] 0 to 1 year** Transfemales (mean [±SD]):	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
United Kingdom Retrospective longitudinal observational single centre study To investigate whether there is any significant loss of bone mineral density (BMD) and bone mineral apparent density (BMAD) for up to 3 years of GnRH analogues. To investigate whether there was a significant drop after 1 year of treatment following abrupt withdrawal. 2011 to 2016	All had been seen and assessed by a Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. All participants had entered puberty and all but 2 of the transmales were postmenarchal. 57% of the transfemales were in early puberty (G2–3 and testicular volume >4 mL) and 43% were in late puberty (G4–5). Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported.	administration reported. No concomitant treatments were reported. No comparator.	0.235 (0.030) g/cm3 at baseline, 0.233 g/cm3 (0.029) at 1 year (p=0.459); z-score 0.859 (0.154) at baseline, −0.228 (1.027) at 1 year (p=0.000) Transmales (mean [±SD]): 0.196 (0.035) g/cm3 at baseline, 0.201 (0.033) g/cm3 at 1 year (p=0.074); z-score −0.186 (1.230) at baseline, −0.541 (1.396) at 1 year (p=0.006) **Lumbar spine BMAD 0 to 2 years** Transfemales (mean [±SD]): 0.240 (0.027) g/cm3 at baseline, 0.240 (0.030) g/cm3 at 2 years (p=0.865); z-score 0.486 (0.809) at baseline, −0.279 (0.930) at 2 years (p=0.000) Transmales (mean [±SD]): 0.195 (0.058) g/cm3 at baseline, 0.198 (0.055) at 2 years (p=0.433); z-score −0.361 (1.439) at baseline, −0.913 (1.318) at 2 years (p=0.001) **Lumbar spine bone mineral density (BMD) 0 to 1 year** Transfemales (mean [±SD]): 0.860 (0.154) kg/m2 at baseline, 0.859 (0.129) kg/m2 at 1 year (p=0.962); z-score −0.016 (1.106) at baseline, −0.461 (1.121) at 1 year (p=0.003) Transmales (mean [±SD]): 0.694 (0.149) kg/m2 at baseline, 0.718 (0.124) kg/m2 at 1 year (p=0.006); z-score −0.395 (1.428) at baseline, −1.276 (1.410) at 1 year (p=0.000) **Lumbar spine BMD 0 to 2 years** Transfemales (mean [±SD]): 0.867 (0.141) kg/m2 at baseline, 0.878 (0.130) kg/m2 at 2 years (p=0.395); z-score 0.130 (0.972) at baseline, −0.890 (1.075) at 2 years (p=0.000) Transmales (mean [±SD]):	1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No **Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes 3. No statement **Overall quality is assessed as poor**. Other comments: although the evidence is of poor quality, the results suggest a possible association between GnRH analogues and BMAD. However, the results are not reliable and could be due to bias or chance. Further details of how the sample was drawn are not reported. No concomitant treatments were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			0.695 (0.220) kg/m2 at baseline, 0.731 (0.209) kg/m2 at 2 years (p=0.058); z-score −0.715 (1.406) at baseline, −2.000 (1.384) at 2 years (p=0.000) ***Bone density: femoral*** **Femoral neck (hip) BMD 0 to 1 year** Transfemales (mean [±SD]): 0.894 (0.118) kg/m2 at baseline, 0.905 (0.104) kg/m2 at 1 year (p=0.571); z-score 0.157 (0.905) at baseline, −0.340 (0.816) at 1 year (p=0.002) Transmales (mean [±SD]): 0.772 (0.137) kg/m2 at baseline, 0.785 (0.120) kg/m2 at 1 year (p=0.797); z-score −0.863 (1.215) at baseline, −1.440 (1.075) at 1 year (p=0.000) **Femoral neck (hip) BMD 0 to 2 years** Transfemales (mean [±SD]): 0.920 (0.116) kg/m2 at baseline, 0.910 (0.125) kg/m2 at 2 years (p=0.402); z-score 0.450 (0.781) at baseline, −0.600 (1.059) at 2 years (p=0.002) Transmales (mean [±SD]): 0.766 (0.215) kg/m2 at baseline, 0.773 (0.197) at 2 years (p=0.604); z-score −1.075 (1.145) at baseline, −1.779 (0.816) at 2 years (p=0.001)	

[1] Lumbar spine (L1-L4) BMD was measured by yearly dual energy X-ray absorptiometry (DXA) scans at baseline (n=70), 1 year (n=70), and 2 years (n=31).
[2] BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. Reported as g/cm3 and z-scores. Hip BMAD z-scores were not calculated as there were no available reference ranges.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Khatchadourian K, Shazhan A, Metzger D. (2014) Clinical management of youth with gender dysphoria in	27 young people with gender dysphoria who started GnRH analogues (at mean age [±SD] 14.7±1.9 years) out of 84 young	**Intervention** 84 young people with gender dysphoria were included. For GnRH analogues no	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Stopping treatment***	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection**

Vancouver. The Journal of Pediatrics 164 (4): 906-11.
 	
Canada
 	
Retrospective observational chart review single centre study
	people seen at the unit between 1998 and 2011.
	Note: the transmale and transfemale subgroups reported in the paper is discrepant, 15 transmales and 11 transfemales (n=26) reported in the outcomes section rather than the n=27 stated in the paper; complete outcome reporting is also incomplete for the transfemale group.
	Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.
		specific treatment, dose or route of administration reported.
		Comparison
		No comparator.
			The authors report that of 15 transmales taking GnRH analogues:
			• 14 transitioned to testosterone treatment during the observation period
			• 7 continued taking GnRH analogues after starting testosterone
			• 7 discontinued GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which:
			  ○ 5 discontinued after hysterectomy and salpingo-oophorectomy
			  ○ 1 discontinued after 2.2 years (transitioned to gender-affirming hormone)
			  ○ 1 discontinued after <2 months due to mood and emotional lability
			The authors report that of 11 transfemales taking GnRH analogues:
			• 5 received oestrogen treatment during the observation period
			• 4 continued taking GnRH analogues during oestrogen treatment
			• 1 discontinued GnRH analogues during oestrogen treatment (no reason reported)
			• 1 stopped GnRH analogues after a few months due to emotional lability
			• 1 stopped GnRH analogues before oestrogen treatment (the following year delayed due to heavy smoking)
			• 1 discontinued GnRH analogues after 13 months due to choosing not to pursue transition
			
			Safety
			Of the 27 patients treated with GnRH analogues:
				1. not reported
				2. no non-exposed cohort
				3. secure record
				4. no
				Domain 2: Comparability
				1. not applicable
				Domain 3: Outcome
				1. record linkage
				2. yes
				3. in complete missing data
				
				Overall quality is assessed as poor.
				
				Other comments: mental health comorbidity was reported for all participants but not for the GnRH analogue cohort separately. Concomitant use of other medicines was not reported.
				
				Source of funding: No source of funding identified.

			• 1 transmale participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale participant developed leg pains and headaches on GnRH analogues, which eventually resolved without treatment. • 1 participant gained 19 kg within 9 months of initiating GnRH analogues, although their body mass index was >85 percentile before GnRH analogues.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of clinical endocrinology and metabolism 100(2): e270-5 Netherlands Retrospective longitudinal observational single centre study To assess BMD development during GnRH analogues and at age 22 years in adolescents with gender dysphoria who started treatment for gender dysphoria during adolescence.	34 adolescents (mean age ±SD 14.9±1.9 for transfemales and 15.0±2.0 for transmales at start of GnRH analogues). Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	The intervention was GnRH analogue monotherapy (triptorelin pamoate 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones from 16 years with discontinuation of GnRH analogue after gonadectomy. Median duration of GnRH analogue monotherapy in transfemales was 1.3 years (range, 0.5 to 3.8 years), and in transmales was 1.5 years	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.22 (0.03) g/cm3, gender-affirming hormones: 0.22 (0.02) g/cm3 (NS); z-score GnRH analogue: −0.44 (1.10), gender-affirming hormones: −0.90 (0.80) (p=NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]: GnRH analogue: 0.25 (0.03) g/cm3, gender-affirming hormones: 0.24 (0.02) g/cm3 (NS);	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group **Domain 3: Outcome** 1. via routine clinical records 2. yes 3. follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor**.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
1998 to 2012		(range, 0.25 to 5.2 years).	z-score GnRH analogue: 0.28 (0.90), gender-affirming hormones: −0.50 (0.81) (p=0.004) **Lumbar spine bone mineral density (BMD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.84 (0.13) g/m2, gender-affirming hormones: 0.84 (0.11) g/m2 (NS); z-score GnRH analogue: −0.77 (0.89), gender-affirming hormones: −1.01 (0.98) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]): GnRH analogue: 0.95 (0.12) g/m2, gender-affirming hormones: 0.91 (0.10) g/m2 (p=0.006); z-score GnRH analogue: 0.17 (1.18), gender-affirming hormones: −0.72 (0.99) (p<0.001) ***Bone density; femoral*** **Femoral area BMAD[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.28 (0.04) g/cm3, gender-affirming hormones: 0.26 (0.04) g/cm3 (NS); z-score GnRH analogue: −0.93 (1.22), gender-affirming hormones: −1.57 (1.74) (p=NS) Change from starting GnRH analogue	Other comments: Within person comparison. Small numbers of participants in each subgroup. No concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			(mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.32 (0.04) g/cm3, gender-affirming hormones: 0.31 (0.04) (NS); z-score GnRH analogue: 0.01 (0.70), gender-affirming hormones: −0.28 (0.74) (NS) **Femoral area BMD[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.88 (0.12) g/m2, gender-affirming hormones: 0.87 (0.08) (NS); z-score GnRH analogue: −0.66 (0.77), gender-affirming hormones: −0.95 (0.63) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.92 (0.10) g/m2, gender-affirming hormones: 0.88 (0.09) (p=0.005); z-score GnRH analogue: 0.36 (0.88), gender-affirming hormones: −0.35 (0.79) (p=0.001)	

[1] BMD and BMAD of the lumbar spine and femoral region (nondominant side) measured by DXA scans at start of GnRH analogues, (n=32), start of gender-affirming hormones (n=34), and at 22 years (n=34).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA et al. (2016)	Adolescents with gender dysphoria (n=116), median age (range) 13.6 years (11.6 to 17.9) in transfemales and 14.2 years (11.1 to	GnRH analogue monotherapy (triptorelin pamoate 3.75 mg at 0, 2 and 4	**Critical outcomes** No critical outcomes assessed. **Important outcomes**	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. The journal of sexual medicine 13(7): 1125-32 Netherlands Prospective longitudinal study To describe the changes in Tanner stage, testicular volume, gonadotropins, and sex steroids during GnRH analogues of adolescents with gender dysphoria to evaluate the efficacy. To report on liver enzymes, renal function and changes in body composition. 1998 to 2009	18.6) in transmales during first year of GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	weeks followed by injections every 4 weeks, route of administration not described) for at least 3 months.	***Other safety outcomes: liver function*** Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment. No values or statistical analyses were reported. ***Other safety outcomes: kidney function*** **Change in serum creatinine between 0 and 1 year** Transfemales (mean [±SD]): 70 (12) micromol/l at baseline, 66 (13) micromol/l at 1 year (p=0.20) Transmales (mean [±SD]): 73 (8) micromol/l at baseline, 68 (13) micromol/l at 1 year (p=0.01)	**Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group **Domain 3: Outcome** 1. via routine clinical records 2. yes 3. no statement **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments or comorbidities were reported. Source of funding: Ferring pharmaceuticals (triptorelin manufacturer)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Staphorsius A, Baudewijntje P, Kreukels P, et al. (2015) Puberty suppression and executive functioning: an fMRI-study	The inclusion criteria were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with	**Intervention** GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact***	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
in adolescents with gender dysphoria. Psychoneuroendocrinology 565:190-9. Netherlands Cross-sectional (single time point) assessment single centre study	measurable oestradiol and testosterone levels in girls and boys, respectively. For all group's exclusion criteria were an insufficient command of the Dutch language (how assessed not reported), unadjusted endocrine disorders, neurological or psychiatric disorders that could lead to deviant test results (details not reported) use of psychotropic medication, and contraindications for an MRI scan. Additionally, adolescents receiving puberty delaying medication or any form of hormones besides oral contraceptives were excluded as controls. The sample size was 85 of whom 41 were adolescents (the numbers are discrepant with the number for whom outcomes are reported n=40) with gender dysphoria (20 of whom were being treated with GnRH analogues); 24 girls and 21 boys without gender dysphoria acted as controls (not further reported here). Details of the sampling frame are not reported. The ages at which GnRH analogues were started was not reported. The mean duration of treatment was 1.6 years (SD 1.0) Mean (±SD) Tanner stage for each group was reported: • Transfemales 3.9 [±1.1] • Transfemales on GnRH analogues 4.1 [±1.0]	subcutaneously or intramuscularly). **Comparison** The comparison was between adolescents with gender dysphoria receiving GnRH analogues and those without GnRH analogues.	The Child Behaviour Checklist (CBCL) was used to assess psychosocial impact. The CBCL was administered once during the study. The reported outcomes for each group were (n, mean [±SD]): • Transfemales (all, n=18) 57.8 [±9.2] • Transfemales on GnRH analogues (n=8) 57.4 [±9.8] • Transfemales without GnRH analogues (n=10) 58.2 [±9.3] • Transmales (all, n=22) 60.4 [±10.2] • Transmales on GnRH analogues (n=12) 57.5 [±9.4] • Transmales without GnRH analogues (n=10) 63.9 [±10.5] The analysis of the CBCL data is not discussed, and statistical analysis is unclear. ***Cognitive development or functioning*** **IQ[1]** • Transfemales (mean [±SD]) on GnRH analogues: 94.0 (10.3) • Transfemales (mean [±SD]) without GnRH analogues: 109.4 (21.2) • Transmales (mean [±SD]) on GnRH analogues: 95.8 (15.6) • Transmales (mean [±SD]) without GnRH analogues: 98.5 (15.9) **Reaction time[2]** • Transfemales (mean [±SD]) on GnRH analogues: 10.9 (4.1) • Transfemales (mean [±SD]) without GnRH analogues: 9.9 (3.1)	1. somewhat representative of children and adolescents who have gender dysphoria 2. drawn from the same community as the exposed cohort 3. via routine clinical records 4. no **Domain 2: Comparability** 1. study controls for age and diagnosis **Domain 3: Outcome** 1. via clinical assessment 2. yes 3. unclear **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This work was supported by an educational grant from the pharmaceutical firm Ferring BV, and by a VICI grant (453-08-003) from the Dutch Science Foundation. The authors state that funding sources did not play a role in any component of this study.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	• Transfemales without GnRH analogues 3.8 [±1.1] • Transmales 4.5 [±0.9] • Transmales on GnRH analogues 4.1 [±1.1] Transmales without GnRH analogues 4.9 [±0.3]		• Transmales (mean [±SD]) on GnRH analogues: 9.9 (3.1) • Transmales (mean [±SD]) without GnRH analogues: 10.0 (2.0) **Accuracy[3]** • Transfemales (mean [±SD]) on GnRH analogues: 73.9 (9.1) • Transfemales (mean [±SD]) without GnRH analogues: 83.4 (9.5) • Transmales (mean [±SD]) on GnRH analogues: 85.7 (10.5) • Transmales (mean [±SD]) without GnRH analogues: 88.8 (9.7)	

[1] Estimated with 4 subscales (arithmetic, vocabulary, picture arrangement, and block design) of the Wechsler Intelligence Scale for Children, third edition (WISC-III®, Wechsler 1991) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III®, Wechsler 1997), depending on the participant's age.
[2] Reaction time in seconds in the Tower of London task
[3] Percentage of correct trials in the Tower of London task

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Vlot, Mariska C, Klink, Daniel T, den Heijer, Martin et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 Netherlands Retrospective observational data analysis study	Adolescents with gender dysphoria, n=70. Median age (range) 15.1 years (11.7 to 18.6) for transmales and 13.5 years (11.5 to 18.3) for transfemales at start of GnRH analogues. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were treated with GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised	GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously).	**Critical outcomes** No critical outcomes reported **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.21 (0.17 to 0.25) g/cm3, gender-affirming hormones: 0.20 (0.18 to 0.24) g/cm3 (NS); z-score GnRH analogue: −0.20 (−1.82 to 1.18), gender-affirming hormones: −1.52 (−2.36 to 0.42) (p=0.001)	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No **Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
To investigate the course of 3 bone turnover markers in relation to bonemineral density, in adolescents with gender dysphoria during GnRH analogue and gender-affirming hormones. 2001 to 2011	participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales group had a bone age of <15 years and the old transfemales group ≥15 years.		Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.22 (0.18 to 0.25) g/cm3, gender-affirming hormones: 0.22 (0.19 to 0.24) g/cm3 (NS); z-score GnRH analogue: −1.18 (−1.78 to 1.09), gender-affirming hormones: −1.15 (−2.21 to 0.08) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.23 (0.20 to 0.29) g/cm3, gender-affirming hormones: 0.23 (0.19 to 0.28) g/cm3 (NS); z-score GnRH analogue: −0.05 (−0.78 to 2.94), gender-affirming hormones: −0.84 (−2.20 to 0.87) (p=0.003) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.26 (0.21 to 0.29) g/cm3, gender-affirming hormones: 0.24 (0.20 to 0.28) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.60 to 1.80), gender-affirming hormones: −0.29 (−2.28 to 0.90) (p≤ 0.0001) ***Bone density; femoral*** **Femoral neck BMAD** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.29 (0.20 to 0.33) g/cm3, gender-affirming hormones: 0.27 (0.20 to 0.33) g/cm3 (p≤0.1); z-score GnRH analogue: −0.71 (−3.35 to	3. Follow-up rate variable across outcomes and no description of those lost **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments were reported. Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			0.37), gender-affirming hormones: −1.32 (−3.39 to 0.21) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.30 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.26 to 0.34) g/cm3 (NS); z-score GnRH analogue: −0.44 (−1.37 to 0.93), gender-affirming hormones: −0.36 (−1.50 to 0.46) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.31 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.22 to 0.35) g/cm3 (NS); z-score GnRH analogue: −0.01 (−1.30 to 0.91), gender-affirming hormones: −0.37 (−2.28 to 0.47) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.33 (0.25 to 0.39) g/cm3, gender-affirming hormones: 0.30 (0.23 to 0.41) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.39 to 1.32), gender-affirming hormones: −0.27 (−1.91 to 1.29) (p=0.002)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa tool for cohort studies

Question	
Domain: Selection	
1. Representativeness of the exposed cohort	Truly representative of the average [describe] in the community Somewhat representative of the average [describe] in the community Selected group of users e.g. nurses, volunteers No description of the derivation of the cohort
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort Drawn from a different source No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	Secure record (e.g. surgical records) Structured interview Written self-report No description
4. Demonstration that outcome of interest was not present at start of study	Yes / No
Domain: Comparability	
1. Comparability of cohorts on the basis of the design or analysis	Study controls for [select most important factor] Study controls for any additional factor [this criteria could be modified to indicate specific control for a second important factor]
Domain: Outcome	
1. Assessment of outcome	Independent blind assessment Record linkage Self-report No description
2. Was follow-up long enough for outcomes to occur	Yes [select and adequate follow up period for outcome of interest] No
3. Adequacy of follow up of cohorts	Complete follow up (all subjects accounted for) Subjects lost to follow up unlikely to introduce bias (small number lost to follow up [select an adequate %] follow up or description provided of those lost) Follow up rate [select an adequate %] and no description of those lost No statement

Appendix G Grade profiles

Table 2: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria									
Mean±SD Utrecht Gender Dysphoria Scale[1] (version(s) not reported), time point at baseline (before GnRH analogues) versus follow-up (before gender-affirming hormones, higher scores indicate more gender dysphoria)									
1 cohort study de Vries et al 2011	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 53.20±7.91 GnRH analogue: 53.9±17.42 *P*=0.333	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.
2 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 3: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Beck Depression Inventory-II, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones). (Lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 8.31±7.12 GnRH analogue: 4.95±6.72 *P*=0.004	Critical	VERY LOW
Mean±SD Trait Anger (TPI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 18.29±5.54 GnRH analogue: 17.88±5.24 *P*=0.503	Critical	VERY LOW
Mean±SD Trait Anxiety (STAI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 39.43±10.07 GnRH analogue: 37.95±9.38 *P*=0.276	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 4: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – body image

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image									
Mean±SD Body Image Scale (primary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 4.10±0.56 GnRH analogue: 3.98±0.71 *P*=0.145	Important	VERY LOW
Mean±SD Body Image Scale (secondary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.74±0.65 GnRH analogue: 2.82±0.68 *P*=0.569	Important	VERY LOW
Mean±SD Body Image Scale (neutral characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.41±0.63 GnRH analogue: 2.47±0.56 *P*=0.620	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 5: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – psychosocial impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline, higher scores indicate benefit)									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 58.72 [±11.38]	n=100 56.63 [±13.14]	*P*=0.23	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 6 months[2] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 60.89 [±12.17]	n=100 60.29 [±12.81]	*P*=0.73	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 12 months[3] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=60 64.70 [±13.34]	n=61 62.97 [±14.10]	*P*=0.49	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 18 months[4] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=35 67.40 [±13.93]	n=36 62.53 [±13.54]	*P*=0.14	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 6 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=101	None	Baseline: 58.72±11.38 6 months: 60.89±12.17 *P*=0.19	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to baseline (higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	Baseline: 58.72±11.38 12 months: 64.70±13.34 *P*=0.003	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	Baseline: 58.72±11.38 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	6 months: 60.89±12.17 12 months: 64.70±13.34 *P*=0.07	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	6 months: 60.89±12.17 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=60 N=35	None	12 months: 64.70±13.34 18 months: 67.40±13.93 *P*=0.35	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 6 months[2] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=201	None	Baseline: 57.73±12.27 6 months: 60.68±12.47 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months[3] compared to baseline (higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	Baseline: 57.73±12.27 12 months: 63.31±14.41 *P*<0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months[4] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	Baseline: 57.73±12.27 18 months: 64.93±13.85 *P*<0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	6 months: 60.68±12.47 12 months: 63.31±14.41 *P*<0.08	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	6 months: 60.68±12.47 18 months: 64.93±13.85 *P*<0.02	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=121 N=71	None	12 months: 63.31±14.41 18 months: 64.93±13.85 *P*<0.45	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, higher scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 70.24±10.12 GnRH analogue: 73.90±9.63 *P*=0.005	Important	VERY LOW
Mean±SD Child Behaviour Checklist (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 60.70±12.76 GnRH analogue: 54.46±11.23 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 61.00±12.21 GnRH analogue: 52.1±9.81 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 58.04±12.99 GnRH analogue: 53.81±11.86 *P*=0.001	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Child Behaviour Checklist total problem scale, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 44.4% GnRH analogue: 22,2% *P*=0.001	Important	VERY LOW
Mean±SD Youth Self-Report (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormone, lower scores indicate benefit).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 55.46±11.56 GnRH analogue: 50.00±10.56 *P*<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 56.04±12.49 GnRH analogue: 49.78±11.63 *P*<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 53.30±11.87 GnRH analogue: 49.98±9.35 *P*=0.009	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 29.6% GnRH analogue: 11.1% *P*=0.017	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transfemales (lower scores indicate benefit									
1 cross-sectional study Staphorsius et al 2015	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=8	N=10	GnRH analogue: 57.4 [±9.8] No GnRH analogue: 58.2 [±9.3]	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transmales (lower scores indicate benefit)									
1 cross-sectional study	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=12	N=10	GnRH analogues: 57.5 [±9.4] No GnRH analogue: 63.9 [±10.5]	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Staphorsius et al 2015									

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 6 months from baseline (after 6 months of psychological support – both groups).
3 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
4 18 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
5 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
6 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 6: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – engagement with healthcare services

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Engagement with healthcare services									
Number (proportion) failing to engage with health care services (did not attend clinic), at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/214 (4.2%)	None	9 adolescents out of 214 failed to attend clinic and were excluded from the study (4.2%)	Important	VERY LOW
Loss to follow-up									
1 cohort study	Serious limitations[2]	No serious indirectness	Not applicable		201	None	The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Costa et al 2015				Not calculable			12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.		

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 7: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – stopping treatment

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Stopping treatment									
Number (proportion) stopping GnRH analogues, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/143 (6.2%)	None	9/143 adolescents stopped GnRH analogues (6.2%)[2]	Important	VERY LOW
Number (proportion) stopping from GnRH analogues, at (up to) 13 years follow-up									
1 cohort study Khatchadourian et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	11/27 (42%)	None	11/26 stopped GnRH analogues (42%)[4]	Important	VERY LOW
Number (proportion) stopping GnRH analogues but who wished to continue endocrine treatment, at (up to) 9 years follow-up									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	4/143 (2.8%)	None	4/143 adolescents stopped GnRH analogues but wished to continue treatment (2.8%)	Important	VERY LOW
Number (proportion) stopping GnRH analogues who no longer wished gender-affirming treatment, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	5/143 (3.5%)	None	5/143 adolescents stopped GnRH analogues and no longer wished to continue gender-affirming treatment (3.5%)	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), although they wanted to continue treatments for gender dysphoria, GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability).
3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).
4 Because of transitioning to gender-affirming hormones or gender-affirming surgery, adverse effects (such as mood and emotional lability) or no longer wishing to pursue transition.

Table 8. Question 2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Bone density: change in lumbar BMAD									
Change in lumbar spine BMAD from baseline to 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), g/cm^3 Baseline: 0.235 (0.030) 1 year: 0.233 (0.029) p=0.459 z-score Baseline: 0.859 (0.154) 1 year: −0.228 (1.027) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), g/cm^3 Baseline: 0.196 (0.035) 1 year: 0.201 (0.033) p=0.074 z-score Baseline: −0.186 (1.230) 1 year: −0.541 (1.396) p=0.006	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), g/cm^3 Baseline: 0.240 (0.027) 2 years: 0.240 (0.030) p=0.865 z-score Baseline: 0.486 (0.809) 2 years: −0.279 (0.930) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transmales									
1 observational study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), g/cm^3 Baseline: 0.195 (0.058) 2 years: 0.198 (0.055) p=0.433	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: −0.361 (1.439) 2 years: −0.913 (1.318) p=0.001		
Change in lumbar BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=11 N=12	None	Mean (SD), g/cm^3 GnRH analogue: 0.22 (0.03) Gender-affirming hormones: 0.22 (0.02) NS z-score GnRH analogue: −0.44 (1.10) Gender-affirming hormones: −0.90 (0.80) p-value: NS	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/cm^3 GnRH analogue: 0.25 (0.03) Gender-affirming hormones: 0.24 (0.02) NS z-score GnRH analogue: 0.28 (0.90) Gender-affirming hormones: −0.50 (0.81) p-value: 0.004	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/cm^3 GnRH analogue: 0.21 (0.17 to 0.25) Gender-affirming hormones: 0.20 (0.18 to 0.24)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							NS z-score GnRH analogue: −0.20 (−1.82 to 1.18) Gender-affirming hormones: −1.52 (−2.36 to 0.42) p-value: <0.01		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/cm^3 GnRH analogue: 0.22 (0.18 to 0.25) Gender-affirming hormones: 0.22 (0.19 to 0.24) NS z-score GnRH analogue: −1.18 (−1.78 to 1.09) Gender-affirming hormones: −1.15 (−2.21 to 0.08) p-value: p≤0.1	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/cm^3 GnRH analogue: 0.23 (0.20 to 0.29) Gender-affirming hormones: 0.23 (0.19 to 0.28) NS z-score GnRH analogue: −0.05 (−0.78 to 2.94) Gender-affirming hormones: −0.84 (−2.20 to 0.87) p-value: ≤0.01	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.26 (0.21 to 0.29) Gender-affirming hormones: 0.24 (0.20 to 0.28) p≤0.01 z-score GnRH analogue: 0.27 (−1.60 to 1.80) Gender-affirming hormones: −0.29 (−2.28 to 0.90) p-value: p ≤ 0.01)	IMPORTANT	VERY LOW
Bone density: change in lumbar BMD									
Change in lumbar spine BMD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.860 (0.154) 1 year: 0.859 (0.129) p=0.962 z-score Baseline: −0.016 (1.106) 1 year: −0.461 (1.121) p=0.003	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.694 (0.149) 1 year: 0.718 (0.124) p=0.006 z-score Baseline: −0.395 (1.428) 1 year: −1.276 (1.410) p=0.000	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar spine BMD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.867 (0.141) 2 years: 0.878 (0.130) p=0.395 z-score Baseline: 0.130 (0.972) 2 years: −0.890 (1.075) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.695 (0.220) 2 years: 0.731 (0.209) p=0.058 z-score Baseline: −0.715 (1.406) 2 years: −2.000 (1.384) p=0.000	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=11	None	Mean (SD), g/m2 GnRH analogue: 0.84 (0.13) Gender-affirming hormones: 0.84 (0.11) NS z-score GnRH analogue: −0.77 (0.89) Gender-affirming hormones: −1.01 (0.98) NS	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/m2 GnRH analogue: 0.95 (0.12) Gender-affirming hormones: 0.91 (0.10) p-value: 0.006 z-score GnRH analogue: 0.17 (1.18) Gender-affirming hormones: −0.72 (0.99) p-value: <0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMD									
Change in femoral neck BMD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.894 (0.118) 1 year: 0.905 (0.104) p=0.571 z-score Baseline: 0.157 (0.905) 1 year: −0.340 (0.816) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 1 year in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.772 (0.137) 1 year: 0.785 (0.120) p=0.797 z-score Baseline: −0.863 (1.215) 1 year: −1.440 (1.075) p=0.000	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.920 (0.116) 2 years: 0.910 (0.125) p=0.402 z-score Baseline: 0.450 (0.781) 2 years: −0.600 (1.059) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.766 (0.215) 2 years: 0.773 (0.197) p=0.604 z-score Baseline: −1.075 (1.145) 2 years: −1.779 (0.816) p=0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMAD									
Change from starting GnRH analogue to starting gender-affirming hormones in femoral neck BMAD in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/cm3 GnRH analogue: 0.29 (0.20 to 0.33) Gender-affirming hormones: 0.27 (0.20 to 0.33) p≤0.1 z-score GnRH analogue: −0.71 (−3.35 to 0.37) Gender-affirming hormones: −1.32 (−3.39 to 0.21) p≤0.1	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/cm3 GnRH analogue: 0.30 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.26 to 0.34) NS z-score GnRH analogue: −0.44 (−1.37 to 0.93) Gender-affirming hormones: −0.36 (−1.50 to 0.46) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/cm3 GnRH analogue: 0.31 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.22 to 0.35) NS z-score GnRH analogue: −0.01 (−1.30 to 0.91) Gender-affirming hormones: −0.37 (−2.28 to 0.47) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.33 (0.25 to 0.39) Gender-affirming hormones: 0.30 (0.23 to 0.41) p-value: ≤0.01 z-score	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							GnRH analogue: 0.27 (−1.39 to 1.32) Gender-affirming hormones: −0.27 (−1.91 to 1.29) p-value: ≤0.01		
Bone density: change in femoral area BMD									
Change in femoral BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=14 N=6	None	Mean (SD), g/m2 GnRH analogue: 0.88 (0.12) Gender-affirming hormones: 0.87 (0.08) NS z-score GnRH analogue: −0.66 (0.77) Gender-affirming hormones: −0.95 (0.63) NS	IMPORTANT	VERY LOW
Change in femoral BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=13	None	Mean (SD), g/m2 GnRH analogue: 0.92 (0.10) Gender-affirming hormones: 0.88 (0.09) p-value: 0.005 z-score GnRH analogue: 0.36 (0.88) Gender-affirming hormones: −0.35 (0.79) p-value: 0.001	IMPORTANT	VERY LOW
Bone density: change in femoral area BMAD									
Change in femoral BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=10	None	Mean (SD), g/cm3 GnRH analogue: 0.28 (0.04) Gender-affirming hormones: 0.26 (0.04) NS z-score GnRH analogue: −0.93 (1.22) Gender-affirming hormones: −1.57 (1.74) p-value: NS	IMPORTANT	VERY LOW
Change in femoral BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=18	None	Mean (SD), g/cm3 GnRH analogue: 0.32 (0.04) Gender-affirming hormones: 0.31 (0.04) NS z-score GnRH analogue: 0.01 (0.70) Gender-affirming hormones: −0.28 (0.74) NS	IMPORTANT	VERY LOW

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; NS, not significant; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Joseph et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no randomisation, no control group and high number of participants lost to follow-up).

3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

Table 9 Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – cognitive development or functioning

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Cognitive development or functioning (1 cross-sectional study)									
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 94.0 (10.3)	N=10 Mean (SD) 109.4 (21.2)	NR	IMPORTANT	VERY LOW
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 95.8 (15.6)	N=10 Mean (SD) 98.5 (15.9)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 10.9 (4.1)	N=10 Mean (SD) 9.9 (3.1)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 9.9 (3.1)	N=10 Mean (SD) 10.0 (2.0)	NR	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Staphorsius et al. 2015									
Accuracy at a single time point between GnRH analogue treated and untreated transfemales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 73.9 (9.1)	N=10 Mean (SD) 83.4 (9.5)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transmales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 85.7 (10.5)	N=10 Mean (SD) 88.8 (9.7)	NR	IMPORTANT	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 10: Question 2: In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Other safety outcomes: change in serum creatinine									
Change in serum creatinine (micromol/l) between baseline and 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=28	None	Mean (SD) Baseline: 70 (12) 1 year: 66 (13) p-value: 0.20	IMPORTANT	VERY LOW
Change in serum creatinine (µmol/l) between baseline and 1 year in transmales									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=29	None	Mean (SD) Baseline: 73 (8) 1 year: 68 (13) p-value: 0.01	IMPORTANT	VERY LOW
Other safety outcomes: liver enzymes									
Presence of elevated liver enzymes (AST, ALT, and glutamyl transferase) between baseline and during treatment									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	39	None	Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment.	IMPORTANT	VERY LOW
Other safety outcomes: adverse effects									
Proportion of patients reporting adverse effects									
1 cohort study Khatchadourian et al 2014	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable[2]	27	None	3/27 adolescents[3]	Important	VERY LOW

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GnRH, gonadotrophin releasing hormone; P, P-value; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Schagen et al. (2016) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

2 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

3 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. 1 transmale developed leg pains and headaches, which eventually resolved without treatment. 1 participant gained 19 kg within 9 months of initiating GnRH analogues.

Table 11: Question 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – critical outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on gender dysphoria									
Mean [±SD] Utrecht Gender Dysphoria Scale (version(s) not reported), time point at baseline (before GnRHa) versus follow-up (just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 47.95 [±9.70] score at T1 49.67 [±9.47]	n-NR[2] score at T0 56.57 [±3.89] score at T1 56.62 [±4.0]	*F*-ratio 15.98 (*df, errdf*: 1,39), *P*<0.001	Critical	VERY LOW
Impact on mental health									
Mean [±SD] Beck Depression Inventory-II, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 5.71 [±4.31] score at T1 3.50 [±4.58]	n-NR[2] score at T0 10.34 [±8.24] score at T1 6.09 [±7.93]	*F*-ratio 3.85 (*df, errdf*: 1,39), *P*=0.057	Critical	VERY LOW
Mean [±SD] Trait Anger (TPI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 5.22 [±2.76] score at T1 5.00 [±3.07]	n-NR[2] score at T0 6.43 [±2.78] score at T1 6.39 [±2.59]	*F*-ratio 5.70 (*df, errdf*: 1,39), *P*=0.022	Critical	VERY LOW
Mean [±SD] Trait Anxiety (STAI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 4.33 [±2.68] score at T1 4.39 [±2.64]	n-NR[2] score at T0 7.00 [±2.36] score at T1 6.17 [±2.69]	*F*-ratio 16.07 (*df, errdf*: 1,39), *P*<0.001	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 The overall sample size completing the outcome at both time points was 41.

Table 11: Question: 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – important outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on body image									
Mean [±SD] Body Image Scale (primary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 4.02 [±0.16] score at T1 3.74 [±0.78]	n-NR[2] score at T0 4.16 [±0.52] score at T1 4.17 [±0.58]	*F*-ratio 4.11 (*df, errdf*: 1,55), *P*=0.047	Important	VERY LOW
Mean [±SD] Body Image Scale (secondary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 2.66 [±0.50] score at T1 2.39 [±0.69]	n-NR[2] score at T0 2.81 [±0.76] score at T1 3.18 [±0.42]	*F*-ratio 11.57 (*df, errdf*: 1,55), *P*=0.001[3]	Important	VERY LOW
Mean [±SD] Body Image Scale (neutral characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 2.60 [±0.58] score at T1 2.32 [±0.59]	n-NR[2] score at T0 2.24 [±0.62] score at T1 2.61 [±0.50]	*F*-ratio 0.081 (*df, errdf*: 1,55), *P*=0.777[3]	Important	VERY LOW
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline.									
1 cohort study Costa et al 2015	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	n=not reported 55.4 [±12.7]	n=not reported 59.2 [±11.8]	*t*-test 2.15; *P*=0.03[5]	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[6] score at T0 73.10 [±8.84] score at T1 77.33 [±8.69]	n-NR[6] score at T0 67.25 [±11.06] score at T1 70.30 [±9.44]	*F*-ratio 5.77 (*df, errdf*: 1,39), *P*=0.021	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 59.42 [±11.78] score at T1 50.38	n-NR[7] score at T0 61.73 [±13.60]	*F*-ratio 2.64 (*df, errdf*: 1,52), *P=0.110*	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
					[±10.57]	score at T1 57.73 [±10.82]			
Mean [±SD] Child Behaviour Checklist (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 60.00 [±9.51] score at T1 52.17 [±9.81]	n-NR[7] score at T0 61.80 [±14.12] score at T1 56.30 [±10.33]	*F*-ratio 1.16 (*df, errdf*: 1,52), *P*=0.286	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (externalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 54.71 [±12.91] score at T1 48.75 [±10.22]	n-NR[7] score at T0 60.70 [±12.64] score at T1 57.87 [±11.66]	*F*-ratio 6.29 (*df, errdf*: 1,52), *P*=0.015	Important	VERY LOW
Mean [±SD] Youth Self-Report (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 53.56 [±12.26] score at T1 47.84 [±10.86]	n-NR[7] score at T0 57.10 [±10.87] score at T1 51.86 [±10.11]	*F*-ratio 1.99 (*df, errdf*: 1,52), *P*=0.164	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Mean [±SD] Youth Self-Report (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 55.88 [±11.81] score at T1 49.24 [±12.24]	n-NR[7] score at T0 56.17 [±13.25] score at T1 50.24 [±11.28]	*F*-ratio 0.049 (*df, errdf*: 1,52), *P*=0.825	Important	VERY LOW
Mean [±SD] Youth Self-Report (externalising T) score, time point at baseline (T0 before GnRHa) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 48.72 [±11.83] score at T1 46.52 [±9.23]	n-NR[7] score at T0 57.24 [±10.59] score at T1 52.97 [±8.51]	*F*-ratio 9.14 (*df, errdf*: 1,52), *P*=0.004	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 The overall sample size completing the outcome at both time points was 57.
3 There was a significant interaction effect between sex assigned at birth and BDI between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary F (df, errdf), P: 14.59 (1,55), P<0.001) and neutral F (df, errdf), P: 15.26 (1,55), P<0.001) sex characteristics compared with sex assigned at birth males.
4 Serious limitations – the cohort study by Costa et al. 2015 was assessed as at high risk of bias (poor quality).
5 At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and females. There were no statistically significant differences in CGAS scores between gender dysphoric sex assigned at birth males and females in all follow-up evaluations (P>0.1; full data not reported).
6 The overall sample size completing the outcome at both time points was 41
7 The overall sample size completing the outcome at both time points was 54.

Glossary

Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating body size measurements using UK norms in growing adolescents.
Child Behaviour Checklist (CBCL)	CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents.
Children's Global Assessment Scale (CGAS)	The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning.
Gender	The roles, behaviours, activities, attributes, and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).
Gonadotrophin releasing hormone (GnRH) analogues	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of 2 gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in FSH and LH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Sex assigned at birth	Sex assigned at birth (male or female) is a biological term and is based on genes and how external and internal sex and reproductive organs work and respond to hormones. Sex is the label that is recorded when a baby's birth is registered.
Tanner stage	Tanner staging is a scale of physical development.
Trait Anger Spielberger scales of the State-Trait Personality Inventory (TPI)	The TPI is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transmale is a person who identifies as male and a transfemale is a person who identifies as female.

Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the impact on gender dysphoria.
Youth Self-Report (YSR)	The self-administered YSR is a checklist to detect emotional and behavioural problems in children and adolescents. It is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour.

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No. 22-11707

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

PAUL A. EKNES-TUCKER, et al.,
Plaintiffs-Appellees,

&

UNITED STATES OF AMERICA
Intervenor-Plaintiff-Appellee,

v.

GOVERNOR OF THE STATE OF ALABAMA, et al.,
Defendants-Appellants.

On Appeal from the United States District Court
for the Middle District of Alabama
Case No. 2:22-cv-184-LCB

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DEFENDANT'S EXHIBIT 10

Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 21 October 2020. See summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Contents

1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see appendix A). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood (World Health Organisation 2020), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves[1] regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics (Diagnostic and Statistical Manual of Mental Disorders 2013).

Gender-affirming hormones are oestradiol for sex assigned at birth males (transfemales) and testosterone for sex assigned at birth females (transmales). The aim of gender-affirming hormones is to induce the development of the physical sex characteristics congruent with the individual's gender expression while aiming to improve mental health and quality of life outcomes.

No oestradiol-containing products are licensed for gender dysphoria and therefore any use for children and adolescents with gender dysphoria is off-label.

The only testosterone-containing product licensed for gender dysphoria is Sustanon 250 mg/ml solution for injection, which is indicated as supportive therapy for transmales, use of all other testosterone-containing products for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, to support young people and their families in managing the uncertainties inherent in gender identity development and to provide ongoing opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of gonadotrophin releasing hormone (GnRH) analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex (NHS England 2013).

Currently NHS England, as part of the Gender Identity Development Service for Children and Adolescents, routinely commissions gender-affirming hormones for young people with continuing gender dysphoria from around their 16th birthday subject to individuals meeting the eligibility and readiness criteria (Clinical Commissioning Policy 2016).

[1] Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men (World Health Organisation, Health Topics: Gender).

2. Executive summary of the review

Ten observational studies were included in the evidence review. Seven studies were retrospective observational studies (Allen et al. 2019, Kaltiala et al. 2020, Khatchadourian et al. 2014, Klaver et Al. 2020, Klink et al. 2015, Stoffers et al. 2019, Vlot et al. 2017) and 3 studies were prospective longitudinal observational studies (Achille et al. 2020, Kuper et al. 2020, Lopez de Lara et al. 2020). No studies directly compared gender-affirming hormones to a control group (either placebo or active comparator). Follow-up was relatively short across all studies, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than saying natal or biological sex and 'cross sex hormones' are now referred to as 'gender-affirming hormones'. The research studies may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are impact on gender dysphoria, impact on mental health and quality of life. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria
The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]) was statistically significantly reduced (improved) from a mean [±SD] score of 57.1 (±4.1) points at baseline to 14.7 (±3.2) points at 12 months, which is below the threshold (40 points) for gender dysphoria ($p<0.001$).

Impact on mental health
Depression
The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, depression (measured using the Beck Depression Inventory-II [BDI-II]) was statistically significantly reduced from a mean [±SD] score of 19.3 (±5.5) points at baseline to 9.7 (±3.9) points at 12 months ($p<0.001$).

The study by Achille et al. 2020 in 50 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, depression was statistically significantly reduced from baseline to about 12 months follow-up:

- The Center for Epidemiologic Studies Depression (CESD-R) improved from a mean score of 21.4 points at baseline to 13.9 points ($p<0.001$).
- The Patient Health Questionnaire (PHQ 9) Modified for Teens improved, although absolute scores were not reported numerically ($p<0.001$).

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria (of whom 123 received gender-affirming hormones) found that during treatment with gender-affirming hormones for an average of 10.9 months, the impact on depression (measured using the Quick Inventory of Depressive Symptoms [QIDS]) was unclear as no statistical analysis was reported. The mean (±SD) self-reported score was 9.6 points (±5.0) at baseline and 7.4 (±4.5) at follow-up. The mean (±SD) clinician-reported score was 5.9 points (±4.1) at baseline and 6.0 (±3.8).

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, statistically significantly fewer participants needed treatment for depression (54% at initial assessment compared with 15% at 12-month follow-up, p<0.001). No details of the treatments for depression are reported.

Anxiety

The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, state anxiety (measured using the State-Trait Anxiety Inventory [STAI] – State subscale) was statistically significantly reduced from a mean (±SD) score of 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). Trait anxiety (measured using STAI – Trait subscale) was also statistically significantly reduced from a mean (±SD) score of 33.0 (±7.2) points at baseline to 18.5 (±8.4) points at 12 months (p<0.001).

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, small reductions were seen in anxiety, panic, generalised anxiety, social anxiety and separation anxiety symptoms and school avoidance (measured using the Screen for Child Anxiety Related Emotional Disorders [SCARED] questionnaire) from baseline to follow-up (mean duration of treatment 10.9 months). The statistical significance of these findings are unknown as no statistical analyses were reported.

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, statistically significantly fewer participants needed treatment for anxiety (48% at initial assessment compared with 15% at 12-month follow-up, p<0.001). No details of treatments for anxiety are reported.

Suicidality and self-injury

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, suicide risk (measured using the Ask Suicide-Screening Questions [ASQ]) was statistically significantly reduced from an adjusted mean (±SE) score of 1.11 points (±0.22) at baseline to 0.27 points (±0.12) after about 12 months (p<0.001).

The study by Achille et al. 2020 in 50 adolescents with gender dysphoria (of whom 35 received gender-affirming hormones at follow-up) found that during treatment with gender-affirming hormones, the impact on suicidal ideation was unclear (measured using the PHQ 9_Modified for Teens with additional questions for suicidal ideation). At baseline 10%of participants had suicidal ideation and 6% had suicidal ideation after about 12 months, but it is unclear if these participants received gender-affirming hormones. No statistical analyses were reported.

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria reported the impact on suicidal ideation, suicide attempts and non-suicidal self-injury during treatment with gender-affirming hormones, after mean 10.9 months follow-up . The statistical significance of these findings are unknown as no statistical analyses were reported:

- Suicidal ideation was reported in 25% of participants 1 month before the initial assessment and in 38% of participants during follow-up.
- Suicide attempts were reported in 2% of participants at 3 months before the initial assessment and in 5% during follow-up.
- Self-injury was reported in 10% of participants at 3 months before the initial assessment and in 17% during follow-up.

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria reported that during treatment with gender-affirming hormones, statistically significantly fewer participants needed treatment for suicidal ideation or self-harm (35% at initial assessment compared with 4% at 12-month follow-up, p<0.001). No details of treatments for suicidal ideation or self-harm are reported.

Other related symptoms

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, there was no statistically significant difference in the number of people needing treatment for either psychotic symptoms or psychosis, conduct problems or antisocial behaviour, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders during the 12-month 'real life' phase compared with before or during the assessment. No details of the treatments received are reported.

Impact on quality of life

The study by Achille et al. 2020 in 50 adolescents with gender dysphoria (of whom 35 were receiving gender-affirming hormones at follow-up) found that during treatment with gender-affirming hormones, quality of life (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire [QLES-Q-SF]) was statistically significantly improved from baseline to about 12 months, but absolute scores were not reported numerically (p<0.001).

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, quality of life (measured using the General Well-Being Scale [GWBS] of the Paediatric Quality of Life Inventory) was statistically significantly improved from an adjusted mean (±SE) score of 61.70 (±2.43) points at baseline to 70.23 (±2.15) points at about 12 months (p<0.002).

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with healthcare services, impact on extent of and satisfaction with surgery and de-transition. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image

The study by Kuper et al. 2020 in 148 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, the impact on body image is unclear (measured using the Body Image Scale [BIS]). The mean (±SD) BIS score was 70.7 points (±15.2) at baseline and 51.4 points (±18.3) at follow-up (mean duration of treatment 10.9 months; no statistical analysis was reported).

Psychosocial impact
The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender affirming hormones, family functioning is unchanged (measured using the Family Adaptability, Partnership, Growth, Affection and Resolve [APGAR] test). The mean score was 17.9 points at baseline and 18.0 points at 12-month follow-up (no statistical analysis was reported).

The study by Lopez de Lara et al. 2020 in 23 adolescents with gender dysphoria found that during treatment with gender affirming hormones, behavioural problems (measured using the Strengths and Difficulties Questionnaire [SDQ]) were statistically significantly improved from a mean (±SD) of 14.7 (±3.3) points at baseline to 10.3 points (±2.9) at 12-month follow-up ($p<0.001$).

The study by Kaltiala et al. 2020 in 52 adolescents with gender dysphoria found that about 12-months after starting treatment with gender-affirming hormones:

- Statistically significantly fewer participants were living with parents or guardians (73% versus 40%, $p=0.001$) and statistically significantly fewer participants had normal peer contacts (89% versus 81%, $p<0.001$).
- There were no statistically significant differences in:
    - progress in school or work (64% versus 60%, $p=0.69$),
    - the number of participants who had been dating or in steady relationships (62% versus 58%, $p=0.51$)
    - the ability to cope with matters outside of the home (for example, shopping and travelling alone on local public transport; 81% versus 81%, $p=1.0$)

Engagement with health care services
No evidence was identified.

Impact on extent of and satisfaction with surgery
No evidence was identified.

De-transition
No evidence was identified.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Important outcomes

The important outcomes for decision making are short- and long-term safety outcomes and adverse effects. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density

The study by Klink et al. 2015 in 34 adolescents with gender dysphoria (who were previously treated with a GnRH analogue) found that gender-affirming hormones may increase lumbar spine and femoral neck bone density. However, not all results are statistically significant (particularly in transfemales). Z-scores suggest the average bone density at the end of follow-up was generally lower than in the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). From starting gender-affirming hormones to age 22 years:

- There was no statistically significant difference in lumbar spine bone mineral apparent density (BMAD) z-score in transfemales, but this was statistically significantly higher in transmales (z-score [±SD]: start of hormones -0.50 [±0.81], age 22 years -0.033 [±0.95], p=0.002).
- There was no statistically significant difference in lumbar spine bone mineral density (BMD) z-score in transfemales or transmales.
- Actual lumbar spine BMAD and BMD values were statistically significantly higher in transfemales and transmales.
- There was no statistically significant difference in femoral neck BMD z-score in transfemales, but this was statistically significantly higher in transmales (z-score [SD]: start of hormones -0.35 [0.79], age 22 years -0.35 [0.74], p=0.006).
- There was no statistically significant difference in actual femoral neck BMAD values in transfemales, but this was statistically significantly higher in transmales.
- Actual femoral neck BMD values were statistically significantly higher in transfemales and transmales.

The study by Vlot et al. 2017 in 70 adolescents with gender dysphoria (who were previously treated with a GnRH analogue) found that gender-affirming hormones may increase lumbar spine and femoral neck bone density. However, not all results are statistically significant. Z-scores suggest the average bone density at the end of follow-up was generally lower than the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). From starting gender-affirming hormones to 24-month follow-up:

- The z-score for lumbar spine BMAD was statistically significantly higher in transfemales with a bone age of less than 15 years (z-score [range]: start of hormones -1.52 [-2.36 to 0.42], 24-month follow-up -1.10 [-2.44 to 0.69], p≤ 0.05) and 15 years and older (z-score [range]: start of hormones -1.15 [-2.21 to 0.08], 24-month follow-up -0.66 [-1.66 to 0.54], p≤ 0.05).
- The z-score for lumbar spine BMAD was statistically significantly higher in transmales with a bone age of less than 14 years (z-score [range]: start of hormones -0.84 [-2.2 to 0.87], 24-month follow-up -0.15 [-1.38 to 0.94], p≤ 0.01) and 14 years and older (z-score [range]: start of hormones -0.29 [-2.28 to 0.90], 24-month follow-up -0.06 [-1.75 to 1.61], p≤ 0.01).
- Actual lumbar spine BMAD values were statistically significantly higher in transfemales and transmales of all bone ages.
- There was no statistically significant difference in femoral neck BMAD z-score in transfemales (all bone ages).

- The z-score for femoral neck BMAD was statistically significantly higher in transmales with a bone age of less than 14 years (z-score [range]: start of hormones -0.37 [-2.28 to 0.47], 24-month follow-up -0.37 [-2.03 to 0.85], p≤ 0.01) and 14 years and older (z-score [range]: start of hormones -0.27 [-1.91 to 1.29], 24-month follow-up 0.02 [-2.1 to 1.35], p≤0.05).
- There was no statistically significant difference in actual femoral neck BMAD values in transfemales (all bone ages), but this was statistically significantly higher in transmales (all bone ages).

The study by Stoffers et al. 2019 in 62 sex assigned at birth females (transmales) with gender dysphoria (who were previously treated with a GnRH analogue) found that during treatment with gender-affirming hormones there was no statistically significant difference in lumbar spine or femoral neck bone density (measured as BMD z-scores or actual values) from starting gender-affirming hormones to any timepoint (6, 12 and 24 months).

Change in clinical parameters

The study by Klaver et al. 2020 in 192 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, from starting treatment to age 22 years:

- Glucose levels, insulin levels and insulin resistance were largely unchanged in transfemales and transmales.
- Total cholesterol, HDL cholesterol and LDL cholesterol levels were unchanged in transfemales, and there was a statistically significant improvement in triglyceride levels.
- Total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels significantly worsened in transmales, but mean levels were within the UK reference range at the end of treatment.
- Diastolic blood pressure was statistically significantly increased in transfemales and transmales. Systolic blood pressure was also statistically significantly increased in transmales, but not in transfemales. The absolute increases in blood pressure were small.
- Body mass index was statistically significantly increased in transfemales and transmales, although most participants were within the healthy weight range (18.5 to 24.9 kg/m).

The study by Stoffers et al. 2019 in 62 sex assigned at birth females (transmales) with gender dysphoria found that during treatment with gender affirming hormones, from starting treatment to 24-month follow-up:

- There was no statistically significant change in glycosylated haemoglobin (HbA1c).
- There was no statistically significant change in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GCT).
- There was a statistically significant increase in alkaline phosphatase (ALP) at some timepoints, but the difference was not statistically significant by 24-months.
- There was a statistically significant increase in serum creatinine levels at all timepoints up to 24 months, but these were within the UK reference range. Serum urea levels were unchanged (follow-up duration not reported).

Treatment discontinuation and adverse effects

The study by Khatchadourian et al. 2014 in 63 adolescents (24 transfemales and 39 transmales) with gender dysphoria found that during treatment with gender affirming hormones (duration of treatment not reported):

- No participants permanently discontinued treatment.
- No transfemales temporarily discontinued treatment, but 3 transmales temporarily discontinued treatment due to mental health comorbidities (n=2) and androgenic alopecia (n=1). All 3 participants eventually resumed treatment, although timescales were not reported
- No severe complications were reported.
- No transfemales reported minor complications, but 12 transmales developed minor complications which were: severe acne (n=7), androgenic alopecia (n=1), mild dyslipidaemia (n=3) and significant mood swings (n=1).

In children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for gender-affirming hormones for children and adolescents with gender dysphoria.

From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria:

- Sex assigned at birth males (transfemales).
- Sex assigned at birth females (transmales).
- Tanner stage at which GnRH analogue or gender-affirming hormones started.
- Diagnosis of a mental health condition.

Some direct comparisons of transfemales and transmales were included. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)
Impact on mental health
In the study by Kuper et al. 2020 in 33 to 45 (number varies by outcome) sex assigned at birth males (transfemales) with gender dysphoria found that during treatment with gender-affirming hormones changes were seen in depression, anxiety and anxiety-related symptoms from baseline to follow-up (mean duration of treatment 10.9 months). The authors did not report any statistical analyses, so it is unclear if any changes were statistically significant.

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, suicide risk (measured using the ASQ) is not statistically significant different in transfemales compared with transmales, between baseline and the final assessment at about 12 months (p=0.79).

The study by Achille et al. 2020 in 17 transfemales with gender dysphoria found that during treatment with gender-affirming hormones, suicidal ideation (measured using the PHQ 9_Modified for Teens with additional questions for suicidal ideation) was reported in 11.8% (2/17) of transfemales at baseline compared with 5.9% (1/17) at about 12-months follow-up (no statistical analysis was reported).

Impact on quality of life
The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, quality of life (measured using the GWBS of the Paediatric Quality of Life Inventory) was not statistically significant different in transfemales compared with transmales, between baseline and the final assessment at about 12 months (p=0.32).

Bone density
The studies by Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in transfemales; see above for details.

Change in clinical parameters
The study by Klaver et al. 2020 provided evidence on the following clinical parameters in transfemales:

- Glucose levels, insulin levels and insulin resistance.
- Total cholesterol, HDL cholesterol and LDL cholesterol and triglycerides.
- Blood pressure.
- Body mass index.

See above for details.

Treatment discontinuation and adverse effects
The study by Khatchadourian et al. 2014 provided evidence on treatment discontinuation and adverse effects in transfemales; see above for details.

Sex assigned at birth females (transmales)
Impact on mental health
In the study by Kuper et al. 2020 in 65 to 78 (number varies by outcome) sex assigned at birth females (transmales) with gender dysphoria found that during treatment with gender-affirming hormones, changes were seen in depression, anxiety and anxiety-related symptoms from baseline to 10.9 month follow-up. The authors did not report any statistical analyses, so it is unclear if any changes were statistically significant.

The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, suicide risk (measured using the ASQ) is not statistically significantly different in transmales compared with transfemales, between baseline and the final assessment (p=0.79).

The study by Achille et al. 2020 in 33 transmales with gender dysphoria found that during treatment with gender-affirming hormones, suicidal ideation (measured using the PHQ 9_Modified for Teens with additional questions for suicidal ideation) was reported in 9.1% (3/33) of transmales at baseline compared with 6.1% (2/33) at about 12-months follow-up (no statistical analysis reported).

Impact on quality of life
The study by Allen et al. 2019 in 47 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, quality of life (measured using the GWBS of the Paediatric Quality of Life Inventory) was not statistically significantly different in transmales compared with transfemales, between baseline and the final assessment at about 12 months (p=0.32).

Bone density
The studies by Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017 provided evidence on bone density in transmales; see above for details.

Change in clinical parameters
The study by Klaver et al. 2020 provided evidence on the following clinical parameters in transmales:

- Glucose levels, insulin levels and insulin resistance.
- Total cholesterol, HDL cholesterol and LDL cholesterol and triglycerides.
- Blood pressure.
- Body mass index.

See above for details.

The study by Stoffers et al. 2019 provided evidence on HbA1c, liver enzymes and renal function in transmales; see above for details.

Treatment discontinuation and adverse effects
The study by Khatchadourian et al. 2014 provided evidence on treatment discontinuation and adverse effects in transmales; see above for details.

Tanner stage at which GnRH analogues or gender-affirming hormones started
The study by Kuper et al. 2020 stated that the impact of Tanner stage on outcomes was considered, but it is unclear if this refers to Tanner stage at the initial assessment, at the start of GnRH analogue treatment or another timepoint. No results were reported.

Diagnosis of a mental health condition
Impact on mental health
The study by Achille et al. 2020 in 50 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, there was no statistically significant difference in depression (measured using the CESD-R and PHQ 9_Modified for Teens) when the results were adjusted for engagement in counselling and medicines for mental health problems, from baseline to about 12-months follow-up.

Impact on quality of life
The study by Achille et al. 2020 in 50 adolescents with gender dysphoria found that during treatment with gender-affirming hormones, there was no statistically significant difference in quality of life (measured using the QLES-Q-SF) when the results were adjusted for engagement in counselling and medicines for mental health problems, from baseline to about 12-months follow-up.

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
(b) what were the ages at which participants commenced treatment with gender-affirming hormones?
(c) what was the duration of treatment with GnRH analogues?

The most commonly reported diagnostic criteria for gender dysphoria was the DSM criteria in use at the time (5/10 studies). In 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017) DSM-IV-TR criteria was used. In 2 studies (Kuper et al. 2020 and Stoffers et al. 2019) DSM-V criteria was used. One study from Finland (Kaltiala et al. 2020) used the ICD-10 diagnosis of 'transexualism'. It was not reported how gender dysphoria was defined in the remaining 4 studies.

In the studies, treatment with gender-affirming hormones started at about 16 to 17 years, with a range of about 14 to 19 years. Most studies did not report the duration of treatment with GnRH analogues, but where this was reported there was a wide variation ranging from a few months up to about 5 years (Klaver et al. 2020, Klink et al. 2015 and Stoffers et al. 2019).

Discussion

The key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies.

All the studies included in the evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes seen were due to gender-affirming hormones or other treatments the participants may have received.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. Furthermore, participant numbers are poorly reported in some studies, with high numbers lost to follow-up or outcomes not reported for some participants. The authors provide no explanation for this incomplete reporting.

Details of the gender-affirming hormone treatment regimen are poorly reported in most of the included studies, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria.

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine whether any statistically significant changes seen are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools (for example, by linking scores to symptom severity), so some conclusions can be made.

Conclusion

Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria.

Results from 5 uncontrolled, observational studies suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty using modified GRADE.

Safety outcomes were reported in 5 observational studies. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are required. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of patients who may benefit more from gender-affirming hormones.

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
   (c) what was the duration of GnRH analogues treatment?

See appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO and were conducted on 21 July 2020.

See appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See appendix C for evidence selection details and appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendix E and appendix F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See appendix G for GRADE Profiles.

4. Summary of included studies

Ten observational studies were included in the evidence review. Seven studies were retrospective observational studies (Allen et al. 2019, Kaltiala et al. 2020, Khatchadourian et al. 2014, Klaver et Al. 2020, Klink et al. 2015, Stoffers et al. 2019, Vlot et al. 2017) and three studies were prospective longitudinal observational studies (Achille et al. 2020, Kuper et al. 2020, Lopez de Lara et al. 2020).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than saying natal or biological sex and 'cross sex hormones' are now referred to as 'gender-affirming hormones'. The research studies may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Achille et al. 2020 Prospective longitudinal study Single centre, New York, United States	50 children, adolescents and young adults with gender dysphoria; 17 transfemales and 33 transmales Mean age at baseline was 16.2 years (SD 2.2)	**Intervention** Endocrine interventions (the collective term used for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for Transgender Health (WPATH) guidelines Puberty suppression was: • GnRH analogue and/or anti-androgens (transfemales) • GnRH analogue or medroxyprogesterone (transmales) Once eligible, gender-affirming hormones were offered, these were: • Oestradiol (transfemales)	**Critical Outcomes** *Impact on mental health* • Depression- The Center for Epidemiologic Studies Depression Scale (CESD-R) • Depression- The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) *Impact on quality of life* • Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) **Important Outcomes** *None reported*

Study	Population	Intervention and comparison	Outcomes reported
		• Testosterone (transmales) Doses and formulations not reported After about 12-months treatment ('wave 3'): • 24 people (48%) were on gender-affirming hormones alone • 12 people (24%) were on puberty suppression alone • 11 people (22%) were on both gender-affirming hormones and puberty suppression • 3 people (6%) were on no endocrine intervention **Comparison** No comparison group. Change over time reported	
Allen et al. 2019 Retrospective longitudinal study Single centre, Kansas City, USA	47 adolescents and young adults with gender dysphoria: 14 transfemales and 33 transmales Mean age at administration (start of treatment) 16.5 years	**Intervention** 39 participants received gender-affirming hormones only 8 participants received hormones and a GnRH analogue Mean duration of treatment with gender-affirming hormones was 349 days (range 113 to 1,016) **Comparison** No comparison group. Comparison over time reported	**Critical Outcomes** *Impact on mental health* • Suicidality- Ask Suicide-Screening Questions (ASQ) instrument *Impact on quality of life* • General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory **Important Outcomes** *None reported*
Kaltiala et al. 2020	52 adolescents with gender dysphoria: 11 transfemales and 41 transmales.	**Intervention** Hormonal sex assignment treatment – details of	**Critical Outcomes** *Impact on mental health*

Study	Population	Intervention and comparison	Outcomes reported
Retrospective chart review Single centre, Tampere, Finland	Mean age at diagnosis 18.1 years (range 15.2 to 19.9)	intervention not reported, although all patients received gender-affirming hormones. **Comparison** No comparison group. Comparison over time reported	• Need for mental health treatment **Important Outcomes** *Psychosocial Impact* Measure of functioning in different domains of adolescent development, which were: • Living with parent(s)/ guardians • Normative peer contacts • Progresses normatively in school/ work • Has been dating or had steady relationships • Is age-appropriately able to deal with matters outside of the home
Khatchadourian et al. 2014 Retrospective chart review Single centre, Vancouver, Canada	84 young people with gender dysphoria, of whom 63 received gender-affirming hormones. Median age at start of gender-affirming hormones was: • 17.3 years (range 13.7-19.8) for testosterone • 17.9 years (range 13.3-22.3) for oestrogen	**Intervention** Transfemales: Oestrogen (oral micronized 17β-oestradiol) Transmales: Testosterone (injectable testosterone enanthate and/or cypionate) 19 participants (30%) had previously received a GnRH analogue **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** *None reported* **Important Outcomes** *Safety:* • Adverse events • Discontinuation rates
Klaver et al. 2020 Retrospective chart review Single centre, Amsterdam, Netherlands	192 people with gender dysphoria who started GnRH analogues before the age of 18 years, and started gender-affirming hormones within 1.5 years of their 22nd birthday.	**Intervention** Oral oestrogen or intramuscular (IM) testosterone **Comparison**	**Critical Outcomes** *None reported* **Important Outcomes** *Safety* • Body mass index (BMI)

Study	Population	Intervention and comparison	Outcomes reported
	Mean age at start of gender-affirming hormones: • Transfemale – 16.4 years (SD 1.1) • Transmale – 16.9 years (SD 1.9)	No comparison group. Comparison over time reported	• Systolic blood pressure • Diastolic blood pressure • Glucose • Insulin • HOMA-IR • Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides
Klink et al. 2015 Retrospective longitudinal study Single centre, Amsterdam, Netherlands	34 young people with gender dysphoria who had received GnRH analogues, gender-affirming hormones and gonadectomy. The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively. At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11) In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0)	**Intervention** Transfemales – oral 17-β oestradiol (incremental dosing) Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing) Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8) The GnRH analogue was subcutaneous (SC) triptorelin 3.75 mg every 4 weeks No details of gonadectomy reported **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** None **Important Outcomes** *Safety* • Bone mineral apparent density (BMAD) • Bone mineral density (BMD) Measures reported at 3 timepoints: start of GnRH analogue treatment, start of gender-affirming hormone treatment and age 22 years.
Kuper et al. 2020 Prospective longitudinal study	Children and adolescents with gender dysphoria (9 to18 years), n=148, of whom: • 25 received puberty suppression only	**Intervention** Gender-affirming hormones, guided by Endocrine Society Clinical Practice Guidelines	**Critical Outcomes** *Impact on mental health* • Depression- Quick Inventory of Depressive

Study	Population	Intervention and comparison	Outcomes reported
Single centre, Texas, USA	• 93 received gender-affirming hormone therapy only • 30 received both Mean age 14.9 years	**Comparison** No comparison group. Comparison over time reported.	Symptoms (QIDS), self-reported • Depression- QIDS, clinician-reported • Anxiety- Screen for Child Anxiety Related Emotional Disorders (SCARED) • Panic- specific questions from SCARED • Generalised anxiety-specific questions from SCARED • Social anxiety - specific questions from SCARED • Separation anxiety-specific questions from SCARED • School avoidance-specific questions from SCARED **Important Outcomes** *Impact on body image* • Body Image Scale (BIS)
Lopez de Lara et al. 2020 Prospective analytical study Single centre, Madrid, Spain	23 adolescents with gender dysphoria: 7 transfemales and 16 transmales. Mean age at baseline was 16 years (range 14 to 18)	**Intervention** Gender-affirming hormones: • Oral oestradiol • Intramuscular testosterone Participants had previously received GnRH analogues in the intermediate pubertal stages (Tanner 2 to 3). Participants were assessed twice: • pre-treatment (T0), • after 12 months treatment with gender-affirming hormones (T1)	**Critical Outcomes** *Impact on gender dysphoria* • Utrecht Gender Dysphoria Scale (UGDS) *Impact on mental health* • Depression- Beck Depression Inventory II (BDI-II) • Anxiety- State-Trait Anxiety Inventory **Important Outcomes** *Psychosocial Impact* • Family functioning-Family APGAR test • Patient strengths and difficulties-Strengths and Difficulties Questionnaire,

Study	Population	Intervention and comparison	Outcomes reported
		Comparison No comparison group. Comparison over time reported.	Spanish Version (SDQ-Cas).
Stoffers et al. 2019 Retrospective chart review Single centre, Leiden, Netherlands	62 transmales with gender dysphoria. Patients had received a GnRH analogue and more than 6 months of testosterone treatment. Median age at start of testosterone was 17.23 years (range 14.9 to 18.4) Median treatment duration was 12 months (range 5 to 33) Change over time	**Intervention** Testosterone intramuscular injections (Sustanon 250 mg). Dose was titrated to a maintenance dose of 125 mg every 2 weeks. Participants who started GnRH analogues at 16 years or older had their dose increased more rapidly. Some participants chose to receive testosterone every 3-4 weeks, and participants could switch to transdermal preparations if needed. **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** None **Important Outcomes** *Safety* • Body mass index (BMI) • Blood pressure • BMD • Acne • Liver enzymes • Creatinine • Urea • HbA1c
Vlot et al. 2017 Retrospective chart review Single centre, Amsterdam, Netherlands	70 children and adolescents with gender dysphoria Median age at baseline – • 13.5 years (11.5-18.3) for transfemales • 15.1 years (range 11.7-18.6) for transmales Comparison is change over time. 24 month follow-up.	**Intervention** Oestrogen or testosterone (had previously received triptorelin for puberty suppression) **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** None **Important Outcomes** *Safety* • Bone mineral apparent density (BMAD)

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	

Critical outcomes	
Impact on gender dysphoria **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective, observational study (Lopez de Lara et al. 2020) provided evidence relating to the impact on gender dysphoria, measured using the Utrecht Gender Dysphoria Scale (UGDS) score during the first year of treatment with gender-affirming hormones. The UGDS is a validated, screening tool for both adolescents and adults, used to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The authors state that the cut-off point to identify gender dysphoria is 40 points. The higher the UGDS score the greater the gender dysphoria. In this study (n=23), the mean (±SD) UGDS score was statistically significantly reduced (improved) from 57.1 (±4.1) points at baseline to 14.7 points (±3.2) at 12 months (p<0.001). A UGDS score below 40 suggests an absence of gender dysphoria **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly improve gender dysphoria from baseline to 12 months follow-up. The mean UGDS score was below the threshold for gender dysphoria at follow-up.**
Impact on mental health: depression **Certainty of evidence: very low**	This is a critical outcome because depression may impact on social, occupational, or other areas of functioning in children and adolescents. Four observational studies (Achille et al. 2020; Kaltiala et al. 2020; Kuper et al. 2020; Lopez de Lara et al. 2020) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria, with follow-up of around 12 months. Five different outcome measures for depression were reported. **Beck Depression Inventory (BDI-II)** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the change in BDI-II. The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. In Lopez de Lara et al. 2020 (n=23) the mean (±SD) BDI-II score was statistically significantly reduced (improved) from 19.3 (±5.5) points at baseline to 9.7 (±3.9) points at 12 months (p<0.001) **(VERY LOW)**. **Center for Epidemiologic Studies Depression (CESD-R)** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in CESD-R scale. The CESD-R is a valid, widely used tool to assess depressive symptoms. Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms. There are no specific scores to categorise depression severity, although the authors of the study suggest that a total CESD-R score less than 16 suggests no clinical depression.

	In Achille et al. 2020 (n=50), the mean CESD-R score statistically significantly reduced (improved) from 21.4 points at baseline to 13.9 points at about 12 months follow-up (p<0.001; standard deviation not reported) **(VERY LOW)**. **Patient Health Questionnaire (PHQ 9) Modified for Teens** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in PHQ 9_Modified for Teens score. The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10 to 14 moderate, 15 to 19 moderately severe, and 20-27 severe symptoms. In Achille et al. 2020 (n=50), the mean PHQ 9_Modified for Teens score statistically significantly reduced (improved) from baseline to around 12 months follow-up, although absolute scores were not reported numerically (p<0.001). From the visual representation of results, the PHQ-9_Modified for Teens score is about 9 at baseline and about 5 at final follow-up **(VERY LOW)**. **Quick Inventory of Depressive Symptoms (QIDS)** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in QIDS, clinician-reported and self-reported. Both the clinician-reported and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 domains (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) added to give a total score ranging from 0 to 27. A score of 0 to 5 suggests no depression, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16 to 20 severe symptoms, and 21 to 27 very severe symptoms. In Kuper et al. 2020 (n=105), the mean (±SD) QIDS self-reported score was 9.6 points (±5.0) at baseline and 7.4 (±4.5) after 10.9 months of treatment with gender-affirming hormones (no statistical analysis reported). The mean (±SD) QIDS clinician-reported score was 5.9 points (±4.1) at baseline and 6.0 (±3.8) after 10.9 months of treatment with gender-affirming hormones (no statistical analysis was reported) **(VERY LOW)**. **Participants needing treatment for depression** One observational study (Kaltiala et al. 2020) reported the proportion of participants needing treatment for depression before or during the initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52), statistically significantly fewer participants needed treatment for depression during the 12-month 'real life' phase (15%, 8/52) compared with before or during the assessment (54%, 28/52; p<0.001). No details of what treatments for depression the participants received are reported **(VERY LOW)**.

	These studies provide very low certainty evidence that during treatment with gender-affirming hormones depression is reduced from baseline to about 12 months follow-up. However, most participants had mild symptoms at the start of treatment.
Impact on mental health: anxiety **Certainty of evidence: very low**	This is a critical outcome because anxiety may impact on social, occupational, or other areas of functioning in children and adolescents. Three observational studies (Kaltiala et al. 2020; Kuper et al. 2020; Lopez de Lara et al. 2020) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. **State-Trait Anxiety Inventory (STAI)** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the change in STAI scores. STAI is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. In Lopez de Lara et al. 2020 (n=23), the mean (±SD) STAI-State subscale was statistically significantly reduced (improved) with gender-affirming hormones from 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). The mean STAI-Trait subscale scores also statistically significantly reduced (improved) from 33.0 points (±7.2) at baseline to 18.5 points (±8.4) at 12 months (p<0.001) **(VERY LOW)**. **Screen for Child Anxiety Related Emotional Disorders (SCARED)** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported anxiety symptoms using the SCARED questionnaire. Other anxiety-related symptoms using specific questions from the SCARED questionnaire were also reported: panic, generalised anxiety, social anxiety, separation anxiety and school avoidance. SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders: • A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these. • A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this. • A score of 5 or more in questions related to separation anxiety may indicate the presence of this. • A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this. • A score of 3 or more in questions related to significant school avoidance may indicate the presence of this. In Kuper et al. 2020 (n=80 to 82, varies by outcome), small reductions were seen in anxiety, panic, generalised anxiety, social anxiety and separation anxiety and school avoidance symptoms (measured using the SCARED questionnaire) from baseline to follow-up (mean duration of treatment 10.9 months). The statistical significance of these findings are unknown as no statistical analyses were reported **(VERY LOW)**.

	Participants needing treatment for anxiety One observational study (Kaltiala et al. 2020) reported the proportion of participants needing treatment for anxiety before or during initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52), statistically significantly fewer participants needed treatment for anxiety during the 12-month 'real life' phase (15%, 8/52) compared with before or during the assessment (48%, 25/52; p<0.001). No details of what treatments for anxiety the participants received are reported **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with gender-affirming hormones anxiety symptoms may be reduced from baseline to around 12 months follow-up.**
Impact on mental health: suicidality and self-injury **Certainty of evidence: very low**	These are critical outcomes because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. Four observational studies (Achille et al. 2020; Allen et al. 2019; Kaltiala et al. 2020; Kuper et al. 2020) provided evidence relating to suicidal ideation in children and adolescents with gender dysphoria, with an average follow-up of around 12 months. **Ask Suicide-Screening Questions (ASQ)** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in ASQ. This is a 4-item dichotomous (yes/no) response measure designed to identify risk of suicide. The authors of Allen et al. 2019 amended 1 question in the ASQ ("*Have you ever tried to kill yourself?*") by prefacing it with "*In the past few weeks . . .*" as they were not investigating lifetime incidence. A response of 'no' is scored as 0 and a response of 'yes' is scored as 1; each item is summed to give an overall score for suicidal ideation ranging from 0 to 4. A person is considered to have screened positive if they answer 'yes' to any item with higher scores indicating higher levels of suicidal ideation. In Allen et al. 2019 (n=39), the adjusted mean (±SE) ASQ score statistically significantly reduced from 1.11 points (±0.22) at baseline to 0.27 points (±0.12) after a mean duration of treatment of about 12 months (p<0.001) **(VERY LOW)**. **PHQ 9_Modified for Teens (additional questions for suicidal ideation)** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in suicidal ideation measured using additional questions from the PHQ 9_Modified for Teens. This is a validated tool to assess depression, dysthymia and suicide risk (see above for detailed description). In addition to the 9 scored questions, the PHQ 9_Modified Teens asked 4 additional questions relating to suicidal ideation and difficulty dealing with problems of life. Responses to the PHQ 9_Modified for Teens were used to determine if the participant had suicidal ideation or not, but specific details of how this was determined are not reported.

	In Achille et al. 2020 (n=50), 10% (5/50) of participants had suicidal ideation at baseline and 6% (3/50) had suicidal ideation after about 12 months treatment with gender-affirming hormones (no statistical analysis reported) **(VERY LOW)**. **Suicidality and non-suicidal self-injury** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported on suicidal ideation, suicide attempts and non-suicidal self-injury, although it was unclear how and when this outcome was measured. In Kuper et al. 2020 (n=130), 25% of participants reported suicidal ideation 1 month before the initial assessment and 38% reported this during the follow-up period (no statistical analysis reported). Suicide attempts were reported in 2% of participants at 3 months before the initial assessment and 5% during follow-up. Self-injury was reported in 10% of participants at 3 months before the initial assessment and 17% during follow-up. No statistical analysis was reported for any outcomes. Mean duration of gender-affirming hormone treatment was 10.9 months **(VERY LOW)**. **Participants needing treatment for suicidality or self-harm** One observational study (Kaltiala et al. 2020) reported the proportion of participants requiring treatment for suicidality or self-harm before or during initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52) statistically significantly fewer participants needed treatment for suicidality or self-harm during the 12-month 'real life' phase (4%, 2/52) compared with before or during the assessment (35%, 18/52; p<0.001). No details of what treatments for suicidal ideation or self-harm the participants received are reported **(VERY LOW)**. **These studies provide very low certainty evidence that gender-affirming hormones may reduce suicidality from baseline to about 12 months follow-up. However, results are inconsistent and it is difficult to draw conclusions.**
Impact on mental health: other **Certainty of evidence: very low**	This is a critical outcome because mental health problems may impact on social, occupational, or other areas of functioning in children and adolescents. One observational study (Kaltiala et al. 2020) reported the proportion of participants needing treatment for either psychotic symptoms or psychosis, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders before or during initial assessment and during the 12-month follow-up period after starting gender-affirming hormones. In Kaltiala et al. 2020 (n=52) there was no statistically significant difference in the number of people needing treatment for either psychotic symptoms / psychosis, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders during the 12-month 'real life' phase compared with before or during the assessment.

	No details of which specific treatments the participants received are reported **(VERY LOW)**. **This study provides very low certainty evidence on the need for treatment for either psychotic symptoms or psychosis, conduct problems or antisocial behaviour, substance abuse, autism, attention deficit hyperactivity disorder (ADHD) or eating disorders during treatment with gender-affirming hormones. No conclusions could be drawn.**
Impact on quality of life score **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Two uncontrolled longitudinal studies Achille et al. 2020; Allen et al. 2019) provided evidence relating to quality of life in children and adolescents with gender dysphoria. **Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)** One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in QLES-Q-SF scores from baseline to about 12 months of treatment with gender-affirming hormones. QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good). In Achille et al. 2020 (n=50), the mean QLES-Q-SF score was statistically significantly reduced from baseline to about 12 months ($p<0.001$). However, absolute scores are not reported numerically **(VERY LOW)**. **General Well-Being Scale (GWBS) of the Paediatric Quality of Life Inventory** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in adjusted mean GWBS of the Paediatric Quality of Life Inventory score from baseline to about 12 months of treatment with gender-affirming hormones. The GWBS of the Paediatric Quality of Life Inventory contains 7 items that measure two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. Higher scores reflect fewer perceived problems and greater well-being. In Allen et al. 2019 (n=47), the adjusted mean (±SE) GWBS of the Paediatric Quality of Life Inventory score was statistically significantly increased (improved) from 61.70 (±2.43) points at baseline to 70.23 (±2.15) points at about 12 months ($p<0.002$) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly improve quality of life and well-being from baseline to 12 months follow-up.**
Important outcomes	
Impact on body image	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of

Certainty of evidence: very low	their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) provided evidence relating to the impact on body image in children and adolescents with gender dysphoria who started treatment with gender-affirming hormones (median duration 10.9 months; range 1 to 18), measured by the change in Body Image Scale (BIS) score. BIS is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. In Kuper et al. 2020 (n=86), the mean (±SD) BIS score was 70.7 points (±15.2) at baseline and 51.4 points (±18.3) at follow-up (no statistical analysis reported) **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on body image during treatment with gender-affirming hormones (mean duration of treatment 10.9 months). No conclusions could be drawn.**
Psychosocial impact **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two uncontrolled, observational studies (Kaltiala et al. 2020; Lopez de Lara et al. 2020) provided evidence related to psychosocial impact in children and adolescents with gender dysphoria. **Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported the Family APGAR test. The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the test: functional, 17 to 20 points; mildly dysfunctional, 16 to 13 points; moderately dysfunctional, 12 to 10 points; severely dysfunctional, <9 points. In Lopez de Lara et al. 2020 (n=23), the mean Family APGAR test score was unchanged from baseline (17.9 points) to 12-month follow-up (18.0 points; no statistical analysis or standard deviations reported) **(VERY LOW)**. **Strengths and Difficulties Questionnaire (SDQ)** One uncontrolled, prospective, analytical study (Lopez de Lara et al. 2020) reported on behaviour using the Strengths and Difficulties Questionnaire (SDQ, Spanish version). The SDQ includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 suggests having a behavioural disorder (normal 0 to 15, borderline 16 to 19, abnormal 20 to 40).

	In Lopez de Lara et al. 2020 (n=23), the mean (±SD) SDQ score was statistically significantly reduced (improved) from 14.7 points (±3.3) at baseline to 10.3 points (±2.9) at 12-month follow-up (p<0.001) **(VERY LOW)**. **Psychosocial functioning** One uncontrolled, retrospective chart review (Kaltiala et al. 2020) reported various markers of functioning in adolescent development, covering living arrangements, peer contacts, school or work progress, relationships, and ability to cope with matters outside the home. These measures were reported during the gender identity assessment and at about 12 months after starting gender-affirming hormones (referred to as the 'real-life phase'). In Kaltiala et al. 2020 (n=52), from the gender identity assessment to the 12-month follow-up period: • statistically significantly fewer participants were living with parents or guardians (73% versus 40%, p=0.001) • statistically significantly fewer participants had normal peer contacts (89% versus 81%, p<0.001) • there was no statistically significant difference in progress in school or work (64% versus 60%, p=0.69) • there was no statistically significant difference in the number of participants who had been dating or in steady relationships (62% versus 58%, p=0.51) • there was no statistically significant difference in the participant's ability to cope with matters outside of the home (81% versus 81%, p=1.00) **(VERY LOW)**. **These studies provide very low certainty evidence that gender-affirming hormones statistically significantly improve behavioural problems (measured by SDQ score). However, the SDQ score was in the 'normal' range at baseline and at 12-month follow up. There was no significant impact on other measures of psychosocial functioning.**
Engagement with health care services	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. No evidence was identified.
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.
De-transition	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria No evidence was identified.

Abbreviations: APGAR: Adaptability, Partnership, Growth, Affection and Resolve; ASQ: Ask Suicide-Screening Questions; BDI-II: Beck Depression Inventory II; BIS: Body Image Scale; CESD-R: Center for Epidemiologic Studies Depression; GWBS: General Well-Being Scale; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QIDS: Quick Inventory of Depressive Symptoms; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SCARED: Screen for Child Anxiety Related Emotional Disorders;

SD: standard deviation; SE: standard error; SDQ: Strengths and Difficulties Questionnaire; STAI: State-Trait Anxiety Inventory; UGDS: Utrecht Gender Dysphoria Scale.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Safety	
Change in bone density: lumbar spine **Certainty of evidence: very low**	This is an important outcome because childhood and adolescence is a key time for bone development and gender-affirming hormones may affect bone development, as shown by changes in lumbar spine bone density. Three uncontrolled, observational studies (2 retrospective and 1 prospective) provided evidence related to bone density: lumbar spine in children and adolescents with gender dysphoria. This was reported as either bone mineral density (BMD), bone mineral apparent density (BMAD), or both. One study reported change in bone density from start of treatment with gender-affirming hormones to age 22 years (Klink et al. 2015). Two studies reported change in bone density from start of gender-affirming hormones up to 24-month follow-up (Stoffers et al. 2019 and Vlot et al. 2017). All participants had previously been treated with a GnRH analogue. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. **Bone mineral apparent density (BMAD)** Two uncontrolled, observational studies reported change in lumbar BMAD (Klink et al. 2015; Vlot et al. 2017). BMAD is a size adjusted value of BMD, incorporating bone size measurements using a UK reference population of growing cis-gender adolescents (up to age 17 years). BMAD is used to correct for height and height gain and may provide a more accurate estimate of bone density in growing adolescents. BMAD was reported as g/cm^3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of -1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. A cis-gender population was used to calculate the bone density z-score, meaning transfemales were compared with cis-males and transmales were compared with cis-females. In Klink et al. 2015 (n=34): • There was no statistically significant difference in lumbar spine BMAD z-score from starting gender-affirming hormones to age 22 years in transfemales. • The z-score for lumbar spine BMAD was statistically significantly higher at age 22 years compared with the start of gender-affirming hormones in transmales (z-score [±SD]: start of hormones -0.50 [±0.81], age 22 years -0.033 [±0.95], p=0.002).

	• Actual lumbar spine BMAD values in g/cm^3 were statistically significantly higher at age 22 years compared with the start of gender-affirming hormones in transfemales and transmales **(VERY LOW)**. In Vlot et al. 2017 (n=70): • The z-score for lumbar spine BMAD in transfemales with a bone age of <15 years was statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones (z-score [range]: start of hormones -1.52 [-2.36 to 0.42], 24-month follow-up -1.10 [-2.44 to 0.69], p≤ 0.05). Statistically significant improvements in z-score for lumbar spine BMAD in transfemales with a bone age of ≥15 years were also seen (z-score [range]: start of hormones -1.15 [-2.21 to 0.08], 24-month follow-up -0.66 [-1.66 to 0.54], p≤ 0.05). • The z-score for lumbar spine BMAD in transmales with a bone age of <14 years was statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones (z-score [range]: start of hormones -0.84 [-2.2 to 0.87], 24-month follow-up -0.15 [-1.38 to 0.94], p≤ 0.01). Statistically significant improvements in z-score for lumbar spine BMAD in transmales with a bone age of ≥14 years were also seen (z-score [range]: start of hormones -0.29 [-2.28 to 0.90], 24-month follow-up -0.06 [-1.75 to 1.61], p≤ 0.01). • Actual lumbar spine BMAD values in g/cm^3 were statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones in transfemales and transmales of all bone ages **(VERY LOW)**. **Bone mineral density (BMD)** Two uncontrolled, observational studies reported change in lumbar BMD (Klink et al. 2015; Stoffers et al. 2019). BMD was determined using dual energy x-ray absorptiometry (DXA-scan; HologicQDR4500, Hologic). BMD was reported as g/cm^2 and as z-scores – see BMAD above for more details). In Klink et al. 2015 (n=34): • There was no statistically significant difference in lumbar spine BMD z-score from starting gender-affirming hormones to age 22 years in transfemales or transmales. • Actual lumbar spine BMD values in g/cm^2 were statistically significantly higher at age 22 years compared with the start of gender-affirming hormones in transfemales and transmales **(VERY LOW)**. In Stoffers et al. 2019 (n=62 at 6-month follow-up; n=15 at 24-month follow-up): • There was no statistically significant difference in lumbar spine BMD z-score in transmales from starting gender-affirming hormones to any timepoint (6, 12 and 24 months). • There was also no statistically significant difference in actual lumbar spine BMD values in g/cm^2 from starting gender-affirming hormones to any timepoint (6, 12 and 24 months) **(VERY LOW)**.

	These studies provide very low certainty evidence that lumber spine bone density (measured by BMAD) increases during treatment with gender-affirming hormones (from baseline to follow-up of 2 to 5 years). Z-scores at the end of follow-up suggest the average lumbar spine bone density was generally lower than the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). The results for bone density (measured by BMD) were inconsistent.
Change in bone density: femoral neck **Certainty of evidence: very low**	This is an important outcome because childhood and adolescence is a key time for bone development and gender-affirming hormones may affect bone development, as shown by changes in femoral neck bone density. Three uncontrolled, observational studies (2 retrospective and 1 prospective) provided evidence related to bone density: femoral neck in children and adolescents with gender dysphoria. This was reported as either bone mineral density (BMD), bone mineral apparent density (BMAD), or both. One study reported change in bone density from start of gender-affirming hormones to age 22 years (Klink et al. 2015). Two studies reported change in bone density from start of gender-affirming hormones up to 24-month follow-up (Stoffers et al. 2019 and Vlot et al. 2017). All participants had previously been treated with a GnRH analogue. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. **Bone mineral apparent density (BMAD)** Two uncontrolled, observational studies reported change in femoral neck BMAD (Klink et al. 2015; Vlot et al. 2017). See above for more details on BMAD. In Klink et al. 2015 (n=34): • The z-score for femoral neck BMAD was reported for the start of gender-affirming hormones but not at age 22 years in transfemales or transmales. No statistical analysis reported. • In transfemales there was no statistically significant difference in actual femoral neck BMAD values in g/cm^3 at age 22 years compared with start of gender-affirming hormones. In transmales actual lumbar spine BMAD values in g/cm^3 were statistically significantly higher at age 22 years compared with start of gender-affirming hormones (mean [±SD]: start of hormones 0.31 [±0.04], age 22 years 0.33 [±0.05], p=0.010) **(VERY LOW)**. In Vlot et al. 2017 (n=70): • In transfemales (all bone ages), there was no statistically significant difference in femoral neck BMAD z-score from start of gender-affirming hormones to 24-month follow-up. • The z-score for femoral neck BMAD in transmales with a bone age of <14 years was statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones (z-score [range]: start of hormones -0.37 [-2.28 to 0.47], 24-month follow-up -0.37 [-2.03 to 0.85], p≤0.01). Statistically significant improvements in z-score for lumbar spine BMAD in transmales with a bone age of ≥14 years were also

	seen (z-score [range]: start of hormones -0.27 [-1.91 to 1.29], 24-month follow-up 0.02 [-2.1 to 1.35], p≤0.05). • In transfemales of all bone ages, there was no statistically significant change in actual femoral neck BMAD values in g/cm^3 from start of gender-affirming hormones to 24-month follow-up. In transmales of all bone ages, actual femoral neck BMAD values in g/cm^3 were statistically significantly higher at 24-month follow-up compared with start of gender-affirming hormones **(VERY LOW)**. **Bone mineral density (BMD)** Two uncontrolled, observational studies reported change in femoral neck BMD (Klink et al. 2015; Stoffers et al. 2019). See above for more details on BMD. In Klink et al. 2015 (n=34): • In transfemales, there was no statistically significant difference in femoral neck BMD z-score from start of gender-affirming hormones to age 22 years. In transmales, femoral neck BMD z-score was statistically significantly higher at age 22 years compared with start of gender-affirming hormones (z-score [SD]: start of hormones -0.35 [0.79], age 22 years -0.35 [0.74], p=0.006). • Actual femoral neck BMD values in g/cm^2 were statistically significantly higher at age 22 years compared with start of gender-affirming hormones in transfemales and transmales **(VERY LOW)**. In Stoffers et al. 2019 (n=62 at 6-month follow-up; n=15 at 24-month follow-up): • there was no statistically significant difference in right or left femoral neck BMD z-score in transmales, from the start of gender-affirming hormones to any timepoint (6, 12 and 24 months). • There was also no statistically significant difference in transmales in right or left actual femoral neck BMD values in g/cm^2 from start of gender-affirming hormones to any timepoint (6, 12 and 24 months) **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with gender-affirming hormones from baseline to follow-up of 2 to 5 years, femoral neck bone density (measured by BMAD) was unchanged in transfemales but was statistically significantly increased in transmales (although the absolute change was small). Z-scores at the end of follow-up suggest that average femoral neck bone density was lower in both transfemales and transmales than in the equivalent cisgender population (transfemales compared with cis-males and transmales compared with cis-females). The results for bone density (measured by BMD) were inconsistent.**
Change in clinical parameters: glucose, insulin and HbA1c	This is an important outcome because the effect of gender-affirming hormones on insulin sensitivity and cardiovascular risk in children and adolescents with gender dysphoria is unknown.

Certainty of evidence: very low	Two uncontrolled, retrospective chart reviews (Klaver et al. 2020; Stoffers et al. 2019) provided evidence on glucose, insulin and HbA1c. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. **Glucose levels, insulin levels and insulin resistance** One retrospective chart review (Klaver et al. 2020) reported non-comparative evidence on the change in glucose levels, insulin levels and insulin resistance (measured using Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) between starting gender-affirming hormones and age 22 years. In Klaver et al. 2020 (n=192): • There was no statistically significant change in glucose levels, insulin levels and insulin resistance in transfemales. • There was no statistically significant change in glucose levels in transmales. • There was a statistically significant decrease in insulin levels in transmales (mean change [95% CI] -2.1 mU/L [-3.9 to -0.3], p<0.05; mean insulin level at 22 years [95% CI] 8.6 mU/L [6.9 to 10.2]). • There was a statistically significant decrease in insulin resistance in transmales (HOMA-IR; mean change [95% CI] -0.5 [-1.0 to -0.1], p<0.05; mean HOMA-IR at 22 years [95% CI] 1.8 [1.4 to 2.2]) **(VERY LOW)**. **HbA1c** One retrospective chart review (Stoffers et al. 2019; n=62) reported non-comparative evidence on the change in HbA1c in transmales between starting gender-affirming hormones and 24-month follow-up. There was no statistically significant change in HbA1c **(VERY LOW)**. **These studies provide very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance.**
Change in clinical parameters: lipids **Certainty of evidence: very low**	This is an important outcome because the effect of gender-affirming hormones on lipid profiles and cardiovascular risk in children and adolescents with gender dysphoria is unknown. One retrospective chart review (Klaver et al. 2020) provided non-comparative evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) between starting gender-affirming hormones and age 22 years. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klaver et al. 2020 (n=192): • There was no statistically significant change in total cholesterol, HDL cholesterol and LDL cholesterol in transfemales. • There was a statistically significant decrease (improvement) in triglycerides in transfemales (mean change [95% CI] +0.2 mmol/L [0.0 to 0.5], p<0.05; mean triglyceride level at 22 years [95% CI] 1.1 mmol/L [0.9 to 1.4]). • There was a statistically significant increase in total cholesterol in transmales (mean change [95% CI] +0.4 mmol/L [0.2 to 0.6],

	p<0.001; mean total cholesterol at 22 years [95% CI] 4.6 mmol/L [4.3 to 4.8]). • There was a statistically significant decrease (worsening) in HDL cholesterol (mean change in transmales [95% CI] -0.3 mmol/L [-0.4 to -0.1], p<0.001; mean HDL cholesterol at 22 years [95% CI] 1.3 mmol/L [1.2 to 1.3]). • There was a statistically significant increase (worsening) in LDL cholesterol in transmales (mean change [95% CI] +0.4 mmol/L [0.2 to 0.6], p<0.001; mean LDL cholesterol at 22 years [95% CI] 2.6 mmol/L [2.4 to 2.8]). • There was a statistically significant increase (worsening) in triglycerides in transmales (mean change [95% CI] +0.5 mmol/L [0.3 to 0.7], p<0.001; mean triglyceride level at 22 years [95% CI] 1.3 mmol/L [1.1 to 1.5]) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones do not affect lipid profiles in transfemales. In transmales, there was a small but statistically significant worsening in cholesterol levels from start of gender-affirming hormone treatment to age 22 years, but mean cholesterol and triglyceride levels were within the UK reference range at the end of treatment.**
Change in clinical parameters: blood pressure **Certainty of evidence: very low**	This is an important outcome because the effect of gender-affirming hormones on blood pressure and cardiovascular risk in children and adolescents with gender dysphoria is unknown. One retrospective chart review (Klaver et al. 2020) provided non-comparative evidence on the change in blood pressure between starting gender-affirming hormones and at age 22 years. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klaver et al. 2020 (n=192): • There was no statistically significant change in systolic blood pressure (SBP) in transfemales. However, there was a statistically significant increase in diastolic blood pressure (DBP) in transfemales (mean change [95% CI] +6 mmHg [3 to 10], p<0.001; mean DBP at 22 years [95% CI] 75 [72 to 78]). • In transmales, there was a statistically significant increase in SBP (mean change [95% CI] +5 mmHg [1 to 9], p<0.05; mean SBP at 22 years [95% CI] 126 [122 to 130]), and DBP (mean change [95% CI] +6 mmHg [4 to 9], p<0.001; mean DBP at 22 years [95% CI] 74 [72 to 77]) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure from start of treatment to age 22 years, although the absolute increase was small.**
Change in clinical parameters: body mass index (BMI)	This is an important outcome because the effect of gender-affirming hormones on weight gain and cardiovascular risk in children and adolescents with gender dysphoria is unknown. One retrospective chart review (Klaver et al. 2020) provided non-comparative evidence on the change in body mass index (BMI) between starting gender-affirming hormones and age 22 years. All

Certainty of evidence: very low	outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klaver et al. 2020 (n=192): • There was a statistically significant increase in BMI in transfemales from the start of gender-affirming hormones to age 22 years (mean change [95% CI] +1.9 [0.6 to 3.2], p<0.005; mean BMI at 22 years [95% CI] 23.2 [21.6 to 24.8]. At age 22 years, 9.9% of transfemales were obese, compared with 3.0% in a reference population of cisgender men. • There was a statistically significant increase in BMI in transmales from the start of gender-affirming hormones to age 22 years (mean change [95% CI] +1.4 [0.8 to 2.0], p<0.005; mean BMI at 22 years [95% CI] 23.9 [23.0 to 24.7]). At age 22 years, 6.6% of transmales were obese, compared with 2.2% in a reference population of cisgender women **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI from start of treatment to age 22 years, although most participants were within the healthy weight range.**
Change in clinical parameters: liver function **Certainty of evidence: very low**	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, gender-affirming hormones may need to be stopped. One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in liver enzymes in transmales between starting gender-affirming hormones and up to 24-months follow-up. In Stoffers et al. 2019 (n=62): • There was no statistically significant change in aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GCT) in transmales. • There was a statistically significant increase in alkaline phosphatase (ALP) levels from starting gender-affirming hormones to 6- and 12-months follow-up, although by 24-months the difference was not statistically significant (median [IQR]: start of hormones 102 [78 to 136], 6-month follow-up 115 [102 to 147] p<0.001, 12-month follow-up 112 [88 to 143] p<0.001) **(VERY LOW)**. **This study provides very low certainty evidence that gender-affirming hormones do not affect liver function in transmales from baseline to 24 months follow-up.**
Change in clinical parameters: kidney function **Certainty of evidence: very low**	This is an important outcome because if renal damage (raised serum creatinine and urea are markers of this) is suspected, treatment with gender-affirming hormones may need to be stopped. One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in serum creatinine and serum urea levels in transmales between starting gender-affirming hormones and up to 24-months follow-up. In Stoffers et al. 2019 (n=62):

	• There was a statistically significant increase in creatinine levels in transmales at all timepoints up to 24 months (mean [SD]: start of hormones 62 umol/L [7], 6 months 70 umol/L [9] , 12 months 74 umol/L [10], 24 months 81 umol/L [10], p<0.001). • There was no statistically significant change in urea in transmales (follow-up duration not reported) **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on kidney function in transmales from baseline to 24 months follow-up. A statistically significant increase in creatinine levels was seen, but these were within the UK reference range. Urea levels were unchanged.**

Treatment discontinuation
 	
Certainty of evidence: very low
	This is an important outcome because there is uncertainty about the short- and long-term impact of stopping treatment with gender-affirming hormones in children and adolescents with gender dysphoria.
	
	One uncontrolled, retrospective chart review (Khatchadourian et al. 2014) provided evidence relating to permanent or temporary treatment discontinuation in children and adolescents with gender dysphoria.
	
	Khatchadourian et al. 2014 narratively reported treatment discontinuation in a cohort of 63 adolescents (24 transfemales and 39 transmales) who received gender-affirming hormones:
	• No participants permanently discontinued gender-affirming hormones.
	• No transfemales temporarily discontinued gender-affirming hormones.
	• Three transmales temporarily discontinued gender-affirming hormones due to:
	  ○ mental health comorbidities (n=2)
	  ○ androgenic alopecia (n=1).
	All 3 participants eventually resumed treatment, although timescales were not reported **(VERY LOW)**.
	
	This study provides very low certainty evidence that the rates of discontinuation during treatment with gender-affirming hormones are low (duration of treatment not reported).

Adverse effects
 	
Certainty of evidence: very low
	This is an important outcome because if there are adverse effects, gender-affirming hormones may need to be stopped.
	
	One uncontrolled, retrospective chart review (Khatchadourian et al. 2014) provided evidence relating to adverse effects from gender-affirming hormones in children and adolescents with gender dysphoria.
	
	Khatchadourian et al. 2014 narratively reported adverse effects in a cohort of 63 adolescents (24 transfemales and 39 transmales) receiving treatment with gender-affirming hormones:
	• No severe complications were reported.
	• No transfemales reported minor complications.
	• Twelve transmales developed minor complications, which were:
	  ○ severe acne, requiring isotretinoin treatment (n=7)
	  ○ androgenic alopecia (n=1)
	  ○ mild dyslipidaemia (further details not provided; n=3)
	  ○ significant mood swings (n=1) **(VERY LOW)**.

	This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones (duration of treatment not reported). No conclusions could be drawn.

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMAD: bone mineral apparent density; BMD: bone mineral density; BMI: body mass index; DBP: diastolic blood pressure; GGT: gamma-glutamyl transferase; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; IQR: interquartile range; LDL: low-density lipoproteins; p: p-value; SBP: systolic blood pressure; SD: standard deviation.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Cost-effectiveness	No studies were identified to assess the cost-effectiveness of gender-affirming hormones for children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from gender-affirming hormones more than the wider population of interest?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). **Impact on mental health: depression and anxiety** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in depression (measured using QIDS clinician-reported and self-reported), anxiety and anxiety-related symptoms (measured using SCARED) in transfemales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=33 to 45, varies by outcome), changes were seen in depression, anxiety and anxiety-related symptoms from baseline to follow-up but the authors did not report any statistical analyses, so it is unclear if was any changes were statistically significant **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on depression, anxiety and anxiety-related symptoms over time in sex assigned at birth males (transfemales; mean duration of treatment 10.9 months). No conclusions could be drawn.** **Impact on mental health: suicidality**

	One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in Ask Suicide-Screening Questions (ASQ) in transfemales compared with transmales. See the clinical effectiveness results above for full details. Between baseline and the final assessment, there was no statistically significant difference in change in ASQ score for transfemales compared with transmales (p=0.79; n=47) **(VERY LOW)**. One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in suicidal ideation in transfemales measured using additional questions from the PHQ 9_Modified for Teens. See the clinical effectiveness results above for full details. At baseline, 11.8% (2/17) of transfemales had suicidal ideation, compared with 5.9% (1/17) at about 12-months follow-up (no statistical analysis reported) **(VERY LOW)**. **These studies provide very low certainty evidence that any change in suicidal ideation is not different between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales) from baseline to follow-up of about 12 months.** **Impact on quality of life** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in the GWBS of the Paediatric Quality of Life Inventory in transfemales compared with transmales. See the clinical effectiveness results above for full details. Between baseline and final assessment, there was no statistically significant difference in change in GWBS of the Paediatric Quality of Life Inventory for transfemales compared with transmales (p=0.32; n=47) **(VERY LOW)**. **This study provides very low certainty evidence that any change in general wellbeing is not different between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales) from baseline to follow-up of about 12 months.** **Impact on body image** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported change in Body Image Scale (BIS) in transfemales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=30), the mean (±SD) BIS score was 67.5 points (±19.5) at baseline and 49.0 points (±21.6) at follow-up (no statistical analysis reported) **(VERY LOW).** **This study provides very low certainty evidence on the effects of gender-affirming hormones on body image over time in transfemales (mean duration of treatment 10.9 months). No conclusions could be drawn.** **Change in bone density: lumbar spine**

	Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on lumber spine bone density in transfemales (Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during treatment with gender-affirming hormones in sex assigned at birth males (transfemales). Z-scores at the end of follow-up suggest average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.** **Change in bone density: femoral neck** Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transfemales (Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) was unchanged in sex assigned at birth males (transfemales) during treatment with gender-affirming hormones (follow-up between 2 and 5 years). Z-scores at the end of follow-up suggest and the average femoral neck bone density was lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.** **Change in clinical parameters: glucose, insulin and HbA1c** One uncontrolled, retrospective chart review (Klaver et al. 2020) provided evidence on glucose, insulin and HbA1c in transfemales. See the safety results table above for a full description of the results. **This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth males (transfemales) from the start of treatment to age 22 years.** **Change in clinical parameters: lipids** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transfemales. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that gender-affirming hormones do not affect lipid profiles in sex assigned at birth males (transfemales) from the start of treatment to age 22 years.** **Change in clinical parameters: blood pressure**

	One retrospective chart review (Klaver et al. 2020) provided evidence on the change in blood pressure in transfemales. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth males (transfemales), although the absolute increase was small from the start of treatment to age 22 years.** **Change in clinical parameters: body mass index (BMI)** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in BMI in transfemales. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth males (transfemales), although most participants were within the healthy weight range from the start of treatment to age 22 years.** **Treatment discontinuation** One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transfemales (Khatchadourian et al. 2014). **This study provides very low certainty evidence that the rates of discontinuation during treatment with gender-affirming hormones in sex assigned at birth males (transfemales) are low. Duration of treatment with gender-affirming hormones was not reported.** **Adverse effects** One uncontrolled, retrospective chart review provided evidence relating to adverse effects from gender-affirming hormones in transfemales (Khatchadourian et al. 2014). **This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth males (transfemales). No conclusions could be drawn. Duration of treatment with gender-affirming hormones was not reported.**
Sex assigned at birth females (transmales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). **Impact on mental health: depression and anxiety** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the change in depression (measured using QIDS clinician-reported and self-reported), anxiety and anxiety-related symptoms (measured using SCARED) in transmales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=65 to 78, varies by outcome), changes were seen in depression, anxiety and anxiety-related symptoms from

	baseline to follow-up but the authors did not report any statistical analysis, so it is unclear if any changes are statistically significant **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on depression, anxiety and anxiety-related symptoms over 10.9 months in transmales. No conclusions could be drawn.** **Impact on mental health: suicidality** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in Ask Suicide-Screening Questions (ASQ) in transmales compared with transfemales. See the sex assigned at birth males (transfemales) row above for full details of the results. One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported the change in suicidal ideation in transmales measured using additional questions from the PHQ 9_Modified for Teens. See the clinical effectiveness results above for full details. At baseline, 9.1% (3/33) of transmales had suicidal ideation, compared with 6.1% (2/33) at about 12-months follow-up (no statistical analysis reported) **(VERY LOW)**. **These studies provide very low certainty evidence that any change in suicidal ideation is not different between sex assigned at birth females (transmales) and sex assigned at birth males (transfemales). Mean duration of treatment about 12 months.** **Impact on quality of life** One uncontrolled, retrospective, longitudinal study (Allen et al. 2019) reported the change in the GWBS of the Paediatric Quality of Life Inventory in transmales compared with transfemales. See the sex assigned at birth males (transfemales) row above for full details of the results. **This study provides very low certainty evidence that any change in general wellbeing is not different between sex assigned at birth females (transmales) and sex assigned at birth males (transfemales). Mean duration of treatment about 12 months.** **Impact on body image** One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported change in Body Image Scale (BIS) in transmales. See the clinical effectiveness results above for full details. In Kuper et al. 2020 (n=66), the mean (±SD) BIS score was 71.1 points (±13.4) at baseline and 52.9 points (±16.8) at follow-up (no statistical analysis reported) **(VERY LOW)**. **This study provides very low certainty evidence on the effects of gender-affirming hormones on body image over 10.9 months in transmales. No conclusions could be drawn.** **Change in bone density: lumbar spine**

	Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on lumber spine bone density in transmales (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). See the safety results table above for a full details of the results. **These studies provide very low certainty evidence that lumbar spine bone density (measured by BMAD) increases during 2 to 5 years treatment with gender-affirming hormones in sex assigned at birth females (transmales). Z-scores at the end of follow-up suggest the average lumbar spine bone density was generally lower than in the equivalent cisgender population. The results for lumbar spine bone density (measured by BMD) were inconsistent.** **Change in bone density: femoral neck** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of gender-affirming hormones on femoral neck bone density in transmales (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). See the safety results table above for a full details of the results. **These studies provide very low certainty evidence that femoral neck bone density (measured by BMAD) statistically significantly increased in sex assigned at birth females (transmales) during 2 to 5 years treatment with gender-affirming hormones. Z-scores at the end of follow-up suggest the average femoral neck bone density was generally lower than in the equivalent cisgender population. The results for femoral neck bone density (measured by BMD) were inconsistent.** **Change in clinical parameters: glucose, insulin and HbA1c** Two uncontrolled, retrospective chart reviews (Klaver et al. 2020; Stoffers et al. 2019) provided evidence on glucose, insulin and HbA1c in transmales. See the safety results table above for full details of the results. **This study provided very low certainty evidence that gender-affirming hormones do not affect HbA1c, glucose levels, insulin levels and insulin resistance in sex assigned at birth females (transmales). Reported from start of treatment to age 22 years.** **Change in clinical parameters: lipids** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) in transmales. See the safety results table above for full details of the results. **This study provides very low certainty evidence that treatment with gender-affirming hormones is associated with a small but statistically significant worsening of cholesterol levels in sex assigned at birth females (transmales), but mean cholesterol and triglyceride levels were within the UK reference range at end of treatment, from start of treatment to age 22 years.**

	Change in clinical parameters: blood pressure One retrospective chart review (Klaver et al. 2020) provided evidence on the change in blood pressure in transmales. See the safety results table above for full details of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase blood pressure in sex assigned at birth females (transmales), although the absolute increase was small, from start of treatment to age 22 years.** **Change in clinical parameters: body mass index (BMI)** One retrospective chart review (Klaver et al. 2020) provided evidence on the change in body mass index (BMI) in transmales. See the safety results table above for full details of the results. **This study provides very low certainty evidence that gender-affirming hormones statistically significantly increase BMI in sex assigned at birth females (transmales), although most participants were within the healthy weight range, from start of treatment to age 22 years.** **Change in clinical parameters: liver function** One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in liver enzymes in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results. **This study provides very low certainty evidence that gender-affirming hormones for about 12 months do not affect liver function in sex assigned at birth females (transmales).** **Change in clinical parameters: kidney function** One retrospective chart review (Stoffers et al. 2019) provided non-comparative evidence on the change in serum creatinine and serum urea levels in transmales between starting gender-affirming hormones and up to 24-months follow-up. See the safety results table above for full details of the results. **This study provides very low certainty evidence on the effects of gender-affirming hormones on kidney function in sex assigned at birth females (transmales). A statistically significant increase in creatinine levels was seen at about 12 months follow-up, but these were within the UK reference range. Urea levels were unchanged.** **Treatment discontinuation** One uncontrolled, retrospective chart review provided evidence relating to permanent or temporary discontinuation of gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results. **This study provides very low certainty evidence that the rates of treatment discontinuation with gender-affirming hormones in sex**

	assigned at birth females (transmales) is low. Duration of gender-affirming hormones not reported. **Adverse effects** One uncontrolled, retrospective chart review provided evidence for adverse effects from gender-affirming hormones in transmales (Khatchadourian et al. 2014). See the safety results table above for full details of the results. **This study provides very low certainty evidence about the potential adverse effects of gender-affirming hormones in sex assigned at birth females (transmales). No conclusions could be drawn. Duration of gender-affirming hormones not reported.**
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at onset of puberty	No evidence was identified.
Tanner stage at which GnRH analogue or gender-affirming hormones started	One uncontrolled, prospective, longitudinal study (Kuper et al. 2020) reported the impact of Tanner stage on outcomes, although it is not clear whether this is referring to Tanner stage at initial assessment, at the start of GnRH analogues or at another timepoint.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of a mental health condition	One uncontrolled, prospective, longitudinal study (Achille et al. 2020) reported outcomes that were adjusted for engagement in counselling and medicines for mental health problems. Information about diagnoses and treatment were not provided. Rates of mental health issues appear to be high in the cohort. **Impact on mental health** Achille et al. 2020 reported the change in depression scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Center for Epidemiologic Studies Depression [CESD-R] scale and Patient Health Questionnaire Modified for Teens [PHQ 9_Modified for Teens] score: • There was no statistically significant change in CESD-R from baseline to about 12-months follow-up. • There was no statistically significant change in PHQ 9_Modified for Teens score from baseline to about 12-months follow-up **(VERY LOW)**. **Impact on quality of life** Achille et al. 2020 reported the change in quality of life scores, controlled for engagement in counselling and medicines for mental health problems (measured using the Quality of Life Enjoyment and Satisfaction Questionnaire [QLES-Q-SF] score: • There was no statistically significant change in QLES-Q-SF score from baseline to about 12-months follow-up **(VERY LOW)**.

	This study provides very low certainty evidence about outcomes that were adjusted for engagement in counselling and medicines for mental health problems. No conclusions could be drawn.

Abbreviations: ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression; GnRH: Gonadotrophin releasing hormone; GWBS: General Well-Being Scale; HDL: high-density lipoproteins; LDL: low-density lipoproteins; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire.

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with gender-affirming hormones?

(c) what was the duration of treatment with GnRH analogues?

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td>Diagnostic criteria</td><td>The DSM-IV-TR criteria was used in 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017).

The DSM-V criteria was used in 2 studies (Kuper et al. 2020 and Stoffers et al. 2019). The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and think of themselves which must have lasted at least 6 months.

The ICD-10 diagnosis of ‘transsexualism’ was used in 1 study (Kaltiala et al. 2020). The authors state that this is the corresponding diagnosis to ‘gender dysphoria’ in the DSM-V, and that diagnostic assessments in the study location (Finland) take place according to ICD-10.

It was not reported how gender dysphoria was defined in the remaining 4 studies (VERY LOW).

From the evidence selected, the most commonly reported diagnostic criteria for gender dysphoria (5/10 studies) was the DSM criteria in use at the time the study was conducted.</td></tr>
<tr><td>Age when gender-affirming hormones started</td><td>8/10 studies reported the age at which participants started treatment with gender-affirming hormones, either as the mean age (with SD) or median age (with the range):

<table>
<tr><th>Study</th><th>Mean age (± SD)</th></tr>
<tr><td>Allen et al. 2019</td><td>16.7 years (not reported)</td></tr>
<tr><td>Khatchadourian et al. 2014</td><td>17.4 years (1.9)</td></tr>
<tr><td>Klaver et al. 2020</td><td>16.4 years (1.1) in transfemales
16.9 years (0.9) in transmales</td></tr>
<tr><td>Kuper et al. 2020</td><td>16.2 (1.2)</td></tr>
<tr><td>Klink et al. 2015</td><td>16.6 years (1.4) in transfemales
16.4 years (2.3) in transmales</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><th>Study</th><th>Median age (range)</th></tr>
<tr><td>Stoffers et al. 2019</td><td>17.2 years (15 to 19.5)</td></tr>
<tr><td>Vlot et al. 2017</td><td>16.3 years (15.9 to 19.5) in transfemales
16.0 years (14.0 to 18.9) in transmales</td></tr>
</table>

Age at the start of treatment was not reported in 3 studies:
• In Achille et al. 2020 the mean age at initial assessment (baseline) was 16.2 years (SD ±2.2)
• In Kaltiala et al. 2020 the mean age at diagnosis was 18.1 years (range 15.2 to 19.9)
• In Lopez de Lara et al. 2020 the mean age of participants was 16 years (range 14 to 18), although it is not clear if this is at the initial assessment or at the start of gender-affirming hormones.

The evidence included showed that most children and adolescents started treatment with gender-affirming hormones at about 16 to 17 years, with a range of about 14 to 19 years.
</td></tr>
<tr><td>Duration of treatment with GnRH analogues</td><td>
The duration of treatment with GnRH analogues was reported in 3/10 studies:

<table>
<tr><th>Study</th><th>Median duration</th></tr>
<tr><td>Klaver et al. 2020</td><td>2.1 years (IQR 1.0 to 2.7) in transfemales
1.0 years (IQR 0.5 to 2.9) in transmales</td></tr>
<tr><td>Klink et al. 2015</td><td>1.3 years (range 0.5 to 3.8) in transfemales
1.5 years (range 0.25 to 5.2) in transmales
(GnRH analogue monotherapy)</td></tr>
<tr><td>Stoffers et al. 2019</td><td>8 months (range 3 to 39)</td></tr>
</table>

The evidence included showed wide variation in the duration of treatment with gender-affirming hormones, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.
</td></tr>
</table>

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; GnRH, Gonadotrophin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies. All the studies included in this evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of gender-affirming hormones, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes observed were due to gender-affirming hormones or other treatments the participants may have received. For example, we do not know if any improvement in depression symptom score over time was the result of gender-affirming hormones or the mental health support the person may be receiving (including medicines or counselling). This may be of particular importance for the mental health outcomes discussed in this review, since depression, anxiety and other related symptoms are common in children and adolescents with gender dysphoria. In Achille et al. 2020, at baseline around one-third of participants were taking medicines for mental health problems and around two-thirds reported being depressed in the past year. In Kaltiala et al. 2020, half the participants needed mental health treatment during and before gender identity assessment, with the most common reasons for treatment being depression, anxiety and suicidality. Only 1 study reported outcomes adjusted for engagement in counselling and medicines for mental health problems (Achille et al. 2020). This study found that gender-affirming hormones had no significant impact on depression and quality of life when adjusted for mental health care, despite significant approvements reported for the unadjusted results. However, it is not possible to draw conclusions on the impact of concurrent mental health treatment on the effect of gender-affirming hormones based on this study alone. Details of the mental health care provided are not reported in the study and results are presented for transfemales and transmales separately, resulting in small patient numbers and possible underpowering.

In most of the included studies, details of the gender-affirming hormone treatment regimens are poorly reported, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria. There is also the suggestion that the hormone dose used in 1 study may have been too low; the authors of Klink et al. 2015 suggest that the relatively low initial dose of oestrogen for transfemales may be the reason for the observed lack of effect on lumber spine bone density. Duration of treatment with a GnRH analogue is also poorly reported and is only stated in 3/10 studies.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. For example, in Kuper et al. 2020 17% of participants received puberty suppression alone, and in Achille et al. 2020, 30% of participants received no treatment or puberty suppression alone. Some results and statistical analyses are only reported for the whole cohort in these studies and not the subgroup of participants who received gender-affirming hormones.

Participant numbers are poorly reported in some of the included studies. In Achille et al. 2020, 47% (45/95) of the people who entered the study did not have follow-up data and were excluded from the analyses, with no explanation or description of those people lost to follow-up. In Kuper et al. 2020, the number of participants varied by outcome, with less than

two-thirds of participants providing data for some outcomes. The authors provide no explanation for this incomplete reporting.

It is not clear whether some outcome measures, specifically those related to psychosocial functioning, are relevant to the UK population. In Kaltiala et al. 2020, an observational study conducted in Finland, the proportion of participants living with parents or guardians is reported as marker of appropriate functioning. The authors state that in Finnish culture young people tend to leave the parental home early, with only around one-quarter of 20 to 24 year olds still living at home. This is lower than in the UK, where around half of 20 to 24 year olds live with their parents or guardians (ONS: Why are more young people living with their parents?).

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. For example, bone density is reported as bone mineral density (BMD) and bone mineral apparent density (BMAD) in the same study, the latter being a size-adjusted measure often useful for people whose bones are still growing. For some populations (transfemale versus transmale) and bone regions (lumber spine versus femoral neck), statistically significant differences in BMD are reported but not for BMAD, and vice versa.

In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine whether any observed statistically significant changes are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools, so some conclusions can be made. For example, the mean Utrecht Gender Dysphoria Scale (UGDS) score (a measure of gender dysphoria symptoms) reduced to about 15 points after treatment with gender-affirming hormones (Lopez de Lara et al. 2020). The authors state that scores of 40 points or above signify gender dysphoria, suggesting that after about 12 months of treatment with gender-affirming hormones, the majority of participants did not have symptoms of gender dysphoria.

The impact of gender-affirming hormones on bone density was reported in 3 studies (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). Although these studies did not include a control group, comparisons to a reference population are reported using z-scores. Comparisons were made to a cisgender population, meaning for example that bone density in transfemales was compared with bone density in cisgender males. The authors of Klink et al. 2015 note that this may not be the ideal comparison, because androgens and oestrogens affect bone differently, and that bone properties in a trans population differ from their age- and sex assigned at birth-matched controls. Beyond this, a major limitation when trying to determine the impact of gender-affirming hormones on the short- and long-term bone health of children and adolescents is the lack of data on fracture rates and other patient-orientated outcomes, including rates of osteoporosis. Studies of GnRH analogues in children and adolescents with gender dysphoria suggest that GnRH analogue treatment may reduce the expected increase in bone density (which is expected during puberty). Although improvements in bone density were reported following treatment with gender-affirming hormones, Z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population.

One study reported on cardiovascular risk factors at age 22 years in people who started gender-affirming hormones for gender dysphoria as adolescents. While glucose levels, insulin levels and insulin resistance were broadly unchanged at 22 years, statistically significant increases in blood pressure and body mass index were seen. A small but statistically significant worsening of the lipid profile in transmales who received testosterone was also seen at age 22 years. However, further studies with a considerably longer follow-up and a focus on patient-oriented outcomes, including cardiovascular events and mortality are needed to determine the long-term impact on cardiovascular health of starting gender-affirming hormones during childhood and adolescence.

Only 1 study reported adverse events and discontinuation rates with gender-affirming hormones in children and adolescents. Conclusions on these outcomes cannot be made based on this study alone.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

7. Conclusion

This evidence review found limited evidence for the effectiveness and safety of gender-affirming hormones in children and adolescents with gender dysphoria, with all studies being uncontrolled, observational studies, and all outcomes of very low certainty. Any potential benefits of treatment must be weighed against the largely unknown long-term safety profile of these treatments.

The results from 5 uncontrolled, observational studies (Achille et al. 2020, Allen et al. 2019, Kaltiala et al. 2020. Kuper et al. 2020, Lopez de Lara et al. 2020) suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty. The clinical relevance of any improvements to the person is difficult to determine because most outcomes do not have a recognised minimal clinically important difference, and the authors do not present statistical analysis for some outcomes.

A further 5 uncontrolled, observational studies (Khatchadourian et al. 2014, Klaver et al. 2020, Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017) reported on safety outcomes, all of which provided very low certainty evidence. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are needed. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

Appendix A PICO

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
   (c) what was the duration of GnRH analogues treatment?

PICO table

P –Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by the study. The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered:

	• Sex assigned at birth males • Sex assigned at birth females • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months) • The age at which treatment was initiated with GnRH analogues and with gender-affirming hormones. • The age of onset of gender dysphoria • The age of onset of puberty • Adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Gender-affirming hormone treatments: • A testosterone preparation for sex assigned at birth female patients which may include testosterone in the form of Sustanon injections*; testosterone enantate injections; Tostran gel*; Testogel; Testim gel; oral testosterone capsules in the form of testosterone undecanoate (Restandol); Andriol testocaps; Nebido • An oestradiol preparation** for sex assigned at birth male patients which may include: oral estradiol valerate*; oestrogen patches (7β-oestradiol patches e.g. Evorel or Estradem); Estradot patches; ethinyloestradiol *** *These are the used by Leeds Hospital, England. ** Be aware that the American spelling is oestrogen without the ‘o’. ***Ethinyloestradiol is rarely used.
C – Comparator(s)	One or a combination of: • Psychological support • Social transitioning to the gender with which the individual identifies. No intervention
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with gender-affirming hormones was initiated • The length of treatment with GnRH analogues where possible. **A: Clinical Effectiveness** *Critical to decision making* • **Impact on gender dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender

	dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measure. • **Impact on Quality of Life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measures. *Important to decision making* • **Impact on body image** This outcome is important because some young people with gender dysphoria may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender. The Body Image Scale could be used as a measure. Other measures as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial Impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up and

	should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery - Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may in adulthood proceed to transitioning surgery. Stated measures of the extent of surgery and satisfaction with surgery in studies may be reported. • **De-transition** The proportion of patients who de-transition following the commencement of gender-affirming hormone treatment and the reasons why. This outcome is important to patients because there is uncertainty about the short and long term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria. **B: Safety** • Short and long -term safety and adverse effects of taking gender-affirming hormones is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long term effects that may impact on decisions for transitioning or de-transitioning. Aspects to be reported on should include Impact of the drug use such as clinically relevant derangement in renal and liver function tests, lipids, glucose, insulin and glycosylated haemoglobin, cognitive development and functioning. The clinical and physical impact of temporary and permanent withdrawal the drug such as when patients decide to de-transition – e.g. delay in the attainment of peak bone mass, attenuation of peak bone mass, permanent physical effects. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 21 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search date: 21 Jul 2020
Number of results retrieved: 650
Search strategy:
Database: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (485)
2 Gender Identity/ (18431)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3134)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (835)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7223)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12665)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102312)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6969)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114785)
13 or/1-12 (252562)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137237)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852126)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1912796)
17 Minors/ (2572)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2360626)
19 exp pediatrics/ (58102)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (835833)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2023650)
22 Puberty/ (13277)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424041)
24 Schools/ (38087)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468784)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89314)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887443)
29 or/14-28 (5532185)
30 13 and 29 (79220)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79220)
33 Hormones/ad, tu, th (4514)
34 exp Progesterone/ad, tu, th (10899)
35 exp Estrogens/ad, tu, th (28936)
36 exp Gonadal Steroid Hormones/ad, tu, th (34137)
37 (progesteron* or oestrogen* or estrogen*).tw. (196074)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (544)
39 exp Estradiol/ad, tu, th (10823)
40 exp Testosterone/ad, tu, th (8318)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (74936)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (90464)
43 or/33-42 (304239)
44 32 and 43 (3183)
45 limit 44 to yr="2000 -Current" (2019)
46 animals/ not humans/ (4685420)
47 45 not 46 (1194)
48 limit 47 to english language (1155)
49 (MEDLINE or pubmed).tw. (163678)
50 systematic review.tw. (121198)
51 systematic review.pt. (130231)
52 meta-analysis.pt. (117148)
53 intervention$.ti. (123904)
54 or/49-53 (380217)
55 randomized controlled trial.pt. (509468)
56 randomi?ed.mp. (796957)
57 placebo.mp. (194937)
58 or/55-57 (848627)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (5562241)
60 ((control and (group* or study)) or (time and factors)).mp. (3274107)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (4624419)
62 or/59-61 (9030680)
63 Observational Studies as Topic/ (5177)
64 Observational Study/ (81866)
65 Epidemiologic Studies/ (8358)

66 exp Case-Control Studies/ (1090891)
67 exp Cohort Studies/ (2011414)
68 Cross-Sectional Studies/ (332273)
69 Controlled Before-After Studies/ (526)
70 Historically Controlled Study/ (185)
71 Interrupted Time Series Analysis/ (913)
72 Comparative Study.pt. (1866044)
73 case control$.tw. (112152)
74 case series.tw. (59119)
75 (cohort adj (study or studies)).tw. (170281)
76 cohort analy$.tw. (6758)
77 (follow up adj (study or studies)).tw. (45131)
78 (observational adj (study or studies)).tw. (86247)
79 longitudinal.tw. (204239)
80 prospective.tw. (495367)
81 retrospective.tw. (442876)
82 cross sectional.tw. (284856)
83 or/63-82 (4368140)
84 54 or 58 or 62 or 83 (9402123)
85 48 and 84 (683)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (33)
87 85 not 86 (650)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 122
Search strategy:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search Strategy:
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1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1473)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2315)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20821)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (963)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15453)
13 or/1-12 (39735)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80295)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (320315)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119124)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (59969)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (68979)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10287)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112220)
29 or/14-28 (523053)
30 13 and 29 (9143)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9144)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (13291)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (241)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (5458)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (4772)
43 or/33-42 (19706)
44 32 and 43 (316)
45 limit 44 to yr="2000 -Current" (303)
46 animals/ not humans/ (1)
47 45 not 46 (303)
48 limit 47 to english language (303)
49 (MEDLINE or pubmed).tw. (36030)
50 systematic review.tw. (29830)
51 systematic review.pt. (1007)
52 meta-analysis.pt. (49)
53 intervention$.ti. (21354)
54 or/49-53 (68976)
55 randomized controlled trial.pt. (277)
56 randomi?ed.mp. (74978)
57 placebo.mp. (18290)
58 or/55-57 (81427)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (455)

60 ((control and (group* or study)) or (time and factors)).mp. (214372)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (339764)
62 or/59-61 (507046)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (91)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (1)
67 exp Cohort Studies/ (1)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (46)
73 case control$.tw. (14451)
74 case series.tw. (13070)
75 (cohort adj (study or studies)).tw. (29119)
76 cohort analy$.tw. (1039)
77 (follow up adj (study or studies)).tw. (3540)
78 (observational adj (study or studies)).tw. (17421)
79 longitudinal.tw. (34485)
80 prospective.tw. (63689)
81 retrospective.tw. (73761)
82 cross sectional.tw. (60195)
83 or/63-82 (250805)
84 54 or 58 or 62 or 83 (687622)
85 48 and 84 (126)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (4)
87 85 not 86 (122)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 32
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search Strategy:
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1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (430)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (637)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1499)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (179)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2460)

13 or/1-12 (4883)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15416)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53285)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22649)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13005)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12420)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1407)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20083)
29 or/14-28 (87968)
30 13 and 29 (1618)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1618)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (1876)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (63)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (846)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (665)
43 or/33-42 (2850)
44 32 and 43 (64)
45 limit 44 to yr="2000 -Current" (61)
46 animals/ not humans/ (0)
47 45 not 46 (61)
48 limit 47 to english language (61)
49 (MEDLINE or pubmed).tw. (7948)
50 systematic review.tw. (7508)
51 systematic review.pt. (28)
52 meta-analysis.pt. (37)
53 intervention$.ti. (4267)
54 or/49-53 (15048)
55 randomized controlled trial.pt. (1)

56 randomi?ed.mp. (14113)
57 placebo.mp. (3097)
58 or/55-57 (15128)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (34)
60 ((control and (group* or study)) or (time and factors)).mp. (31615)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (65735)
62 or/59-61 (88222)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (4)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (0)
67 exp Cohort Studies/ (0)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (0)
73 case control$.tw. (2577)
74 case series.tw. (2480)
75 (cohort adj (study or studies)).tw. (7959)
76 cohort analy$.tw. (287)
77 (follow up adj (study or studies)).tw. (632)
78 (observational adj (study or studies)).tw. (3763)
79 longitudinal.tw. (7079)
80 prospective.tw. (12148)
81 retrospective.tw. (16600)
82 cross sectional.tw. (9459)
83 or/63-82 (48534)
84 54 or 58 or 62 or 83 (119752)
85 48 and 84 (32)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (32)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 22 July 2020
Number of results retrieved: 3
Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search Strategy:
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1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (22)

9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Hormones/ad, tu, th (3)
34 exp Progesterone/ad, tu, th (3)
35 exp Estrogens/ad, tu, th (8)
36 exp Gonadal Steroid Hormones/ad, tu, th (22)
37 (progesteron* or oestrogen* or estrogen*).tw. (161)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (3)
39 exp Estradiol/ad, tu, th (8)
40 exp Testosterone/ad, tu, th (8)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (79)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (61)
43 or/33-42 (261)
44 32 and 43 (7)
45 limit 44 to yr="2000 -Current" (7)
46 animals/ not humans/ (3647)
47 45 not 46 (6)
48 limit 47 to english language (6)
49 (MEDLINE or pubmed).tw. (529)
50 systematic review.tw. (512)

51 systematic review.pt. (522)
52 meta-analysis.pt. (370)
53 intervention$.ti. (247)
54 or/49-53 (1065)
55 randomized controlled trial.pt. (595)
56 randomi?ed.mp. (1203)
57 placebo.mp. (219)
58 or/55-57 (1234)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7958)
60 ((control and (group* or study)) or (time and factors)).mp. (4307)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (5828)
62 or/59-61 (11814)
63 Observational Studies as Topic/ (27)
64 Observational Study/ (449)
65 Epidemiologic Studies/ (7)
66 exp Case-Control Studies/ (2173)
67 exp Cohort Studies/ (3287)
68 Cross-Sectional Studies/ (837)
69 Controlled Before-After Studies/ (1)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (6)
72 Comparative Study.pt. (768)
73 case control$.tw. (182)
74 case series.tw. (139)
75 (cohort adj (study or studies)).tw. (561)
76 cohort analy$.tw. (22)
77 (follow up adj (study or studies)).tw. (40)
78 (observational adj (study or studies)).tw. (253)
79 longitudinal.tw. (429)
80 prospective.tw. (778)
81 retrospective.tw. (1032)
82 cross sectional.tw. (739)
83 or/63-82 (5471)
84 54 or 58 or 62 or 83 (12581)
85 48 and 84 (3)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (3)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23 July 2020
Number of results retrieved: 1207
Search strategy:

Database: Embase <1974 to 2020 July 22>
Search Strategy:
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1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)

6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ (1108)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (12470)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (581748)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ or adolescent health/ or middle school student/ or high school student/ (3440943)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)
25 or/14-24 (7130881)
26 13 and 25 (181778)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (17)
28 26 or 27 (181778)
29 hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (5160)
30 exp progesterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (23479)
31 exp estrogen/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (57641)
32 steroid hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (372)
33 sex hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (1984)
34 hormonal therapy/ (42222)
35 (progesteron* or oestrogen* or estrogen*).tw. (254142)
36 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (1224)
37 exp estradiol derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (30740)

38 exp testosterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (15868)
39 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (99596)
40 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (114290)
41 or/29-40 (438737)
42 28 and 41 (6053)
43 limit 42 to yr="2000 -Current" (4741)
44 nonhuman/ not human/ (4649157)
45 43 not 44 (3636)
46 limit 45 to english language (3513)
47 (MEDLINE or pubmed).tw. (261145)
48 exp systematic review/ or systematic review.tw. (302985)
49 meta-analysis/ (191173)
50 intervention$.ti. (200041)
51 or/47-50 (660206)
52 random:.tw. (1552336)
53 placebo:.mp. (455979)
54 double-blind:.tw. (210671)
55 or/52-54 (1807280)
56 cohort analysis/ (596360)
57 exp epidemiology/ (3434332)
58 exp clinical trial/ (1504711)
59 evaluation study/ (45870)
60 statistics/ (301181)
61 ((control and (group* or study)) or (time and factors)).mp. (3324555)
62 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (6067112)
63 or/56-62 (11048972)
64 Clinical study/ (155444)
65 Case control study/ (157943)
66 Family study/ (26047)
67 Longitudinal study/ (141660)
68 Retrospective study/ (937696)
69 comparative study/ (859061)
70 Prospective study/ (613138)
71 Randomized controlled trials/ (182542)
72 70 not 71 (606604)
73 Cohort analysis/ (596360)
74 cohort analy$.tw. (13020)
75 (Cohort adj (study or studies)).tw. (302159)
76 (Case control$ adj (study or studies)).tw. (137432)
77 (follow up adj (study or studies)).tw. (63423)
78 (observational adj (study or studies)).tw. (168428)
79 (epidemiologic$ adj (study or studies)).tw. (106448)
80 (cross sectional adj (study or studies)).tw. (220073)
81 case series.tw. (104089)
82 prospective.tw. (861922)
83 retrospective.tw. (886445)
84 or/64-69,72-83 (4047788)
85 51 or 55 or 63 or 84 (12494560)
86 46 and 85 (2151)
87 86 not (letter or editorial).pt. (2137)

88 87 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (1207)

Database: APA PsycInfo

Platform: Ovid
Version: APA PsycInfo <1806 to July Week 2 2020>
Search date: 22 July 2020
Number of results retrieved: 581
Search strategy:

Database: APA PsycInfo <1806 to July Week 2 2020>
Search Strategy:
---
1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15276)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99498)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)
14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ (29181)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1765408)
26 11 and 25 (49560)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)

28 26 or 27 (49561)
29 hormones/ (8408)
30 sex hormones/ (1777)
31 exp progestational hormones/ (2409)
32 estrogens/ (3889)
33 steroids/ (3797)
34 (progesteron* or oestrogen* or estrogen*).tw. (11188)
35 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (457)
36 estradiol/ (3120)
37 testosterone/ (5606)
38 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (9625)
39 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (6741)
40 or/29-39 (30344)
41 28 and 40 (1005)
42 limit 41 to yr="2000 -Current" (749)
43 limit 42 to english language (692)
44 limit 43 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (111)
45 43 not 44 (581)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 22 July 2020
Number of results retrieved: CDSR 0 ; CENTRAL 67.

ID Search Hits
#1 MeSH descriptor: [Gender Dysphoria] this term only 3
#2 MeSH descriptor: [Gender Identity] this term only 227
#3 MeSH descriptor: [Sexual and Gender Disorders] this term only 2
#4 MeSH descriptor: [Transsexualism] this term only 27
#5 MeSH descriptor: [Transgender Persons] this term only 36
#6 MeSH descriptor: [Health Services for Transgender Persons] this term only 0
#7 MeSH descriptor: [Sex Reassignment Procedures] explode all trees 4
#8 (gender* near/3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab,kw 702
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab,kw 959
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab,kw 3969
#11 ((sex or gender*) near/3 (reassign* or chang* or transform* or transition*)):ti,ab,kw 524
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab,kw 516
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 6413
#14 MeSH descriptor: [Infant] explode all trees 28440
#15 MeSH descriptor: [Infant Health] this term only 49
#16 MeSH descriptor: [Infant Welfare] this term only 82

#17 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab,kw,so 89530
#18 MeSH descriptor: [Child] explode all trees 44089
#19 MeSH descriptor: [Child Behavior] explode all trees 2061
#20 MeSH descriptor: [Child Health] this term only 98
#21 MeSH descriptor: [Child Welfare] this term only 325
#22 MeSH descriptor: [Minors] this term only 8
#23 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 265417
#24 MeSH descriptor: [Pediatrics] explode all trees 661
#25 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 57725
#26 MeSH descriptor: [Adolescent] this term only 102154
#27 MeSH descriptor: [Adolescent Behavior] this term only 1358
#28 MeSH descriptor: [Adolescent Health] this term only29
#29 MeSH descriptor: [Puberty] this term only 295
#30 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab,kw,so 140927
#31 MeSH descriptor: [Schools] this term only 1914
#32 MeSH descriptor: [Child Day Care Centers] this term only 231
#33 MeSH descriptor: [Nurseries, Infant] explode all trees 17
#34 MeSH descriptor: [Schools, Nursery] this term only 37
#35 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw,so 97810
#36 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near/2 (year or years or age or ages or aged)):ti,ab 6710
#37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near/2 (year or years or age or ages or aged)):ti,ab 196881
#38 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 516067
#39 #13 and #38 2488
#40 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab,kw 0
#41 #39 or #40 2488
#42 MeSH descriptor: [Hormones] this term only 2241
#43 MeSH descriptor: [Progesterone] explode all trees 3135
#44 MeSH descriptor: [Estrogens] explode all trees 1841
#45 MeSH descriptor: [Gonadal Steroid Hormones] explode all trees 10747
#46 (progesteron* or oestrogen* or estrogen*):ti,ab,kw 18387
#47 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)):ti,ab,kw 24
#48 MeSH descriptor: [Estradiol] explode all trees 4434
#49 MeSH descriptor: [Testosterone] explode all trees 2945
#50 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan):ti,ab,kw 7386
#51 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle):ti,ab,kw 11410
#52 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 31870
#53 #41 and #52 121
#54 "conference":pt or (clinicaltrials or trialsearch):so 492465
#55 #53 not #54 72

Database: HTA

Platform: Wiley
Version: up to 2018
Search date: 22nd July 2020
Number of results retrieved: 4
Search strategy:

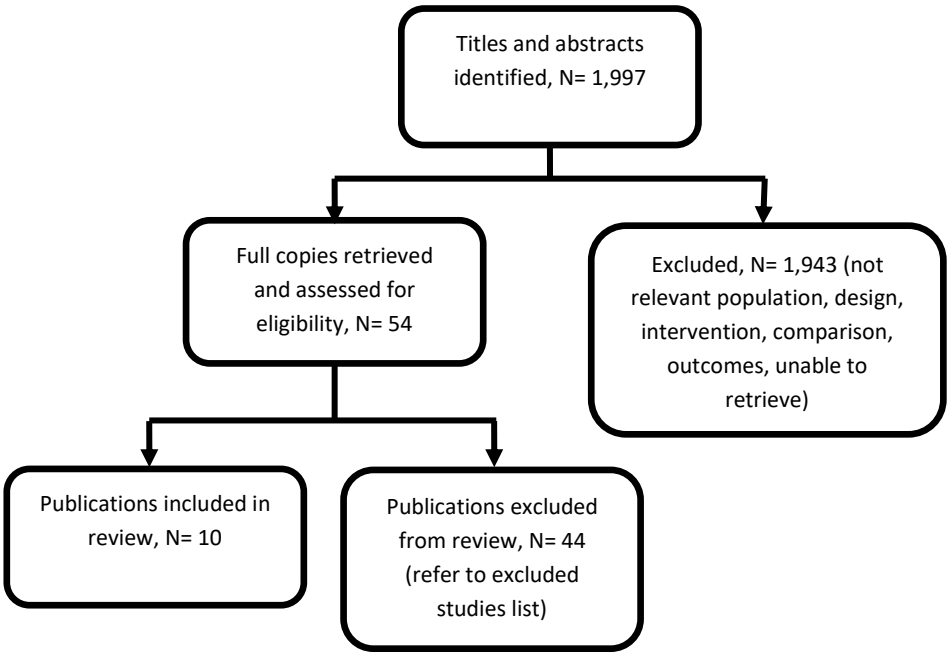
#1 MeSH DESCRIPTOR Gender Dysphoria 0
#2 MeSH DESCRIPTOR Gender Identity 12
#3 MeSH DESCRIPTOR Sexual and Gender Disorders 2
#4 MeSH DESCRIPTOR Transsexualism 12
#5 MeSH DESCRIPTOR Transgender Persons 3
#6 MeSH DESCRIPTOR Health Services for Transgender Persons 0
#7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1
#8 ((gender* near3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*))) 28
#9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
#10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
#11 (((sex or gender*) near3 (reassign* or chang* or transform* or transition*))) 24
#12 ((male-to-female or m2f or female-to-male or f2m)) 86
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 261
#14 MeSH DESCRIPTOR Infant EXPLODE ALL TREES 2964
#15 MeSH DESCRIPTOR Infant Health 0
#16 MeSH DESCRIPTOR Infant Welfare 22
#17 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*)) 5510
#18 MeSH DESCRIPTOR Child EXPLODE ALL TREES 4935
#19 MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES 64
#20 MeSH DESCRIPTOR Child Health 2
#21 MeSH DESCRIPTOR Child Welfare 80
#22 MeSH DESCRIPTOR Minors 2
#23 ((child* or minor or minors or boy* or girl* or kid or kids or young*)) 13575
#24 MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES 119
#25 ((pediatric* or paediatric* or peadiatric*)) 2842
#26 MeSH DESCRIPTOR Adolescent 4594
#27 MeSH DESCRIPTOR Adolescent Behavior 94
#28 MeSH DESCRIPTOR Adolescent Health 0
#29 MeSH DESCRIPTOR Puberty 3
#30 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)) 5621
#31 MeSH DESCRIPTOR Schools 168
#32 MeSH DESCRIPTOR Child Day Care Centers 12
#33 MeSH DESCRIPTOR Schools, Nursery 3
#34 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)) 4454
#35 ((("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near2 (year or years or age or ages or aged))) 380
#36 ((("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near2 (year or years or age or ages or aged))) 7996

#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 22640
#38 #13 AND #37 116
#39 (#13 AND #37) IN HTA 4

Appendix C Evidence selection

The literature searches identified 1,997 references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 10 references are included in the evidence review. The remaining 44 references were excluded and are listed in appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aranda G, Mora M, Hanzu FA et al. (2019) Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. Endocrinologia, diabetes y nutricion 66(6): 385–392	Excluded on population – adult study, participants not 18 years or less (mean age 27.1 years).
Arnold, Justin D, Sarkodie, Eleanor P, Coleman, Megan E et al. (2016) Incidence of Venous Thromboembolism in Transgender Women	Excluded on population – adult study, participants not 18 years or less (mean age 33.2 years).

Study reference	Reason for exclusion
Receiving Oral Estradiol. The journal of sexual medicine 13(11): 1773–1777	
Asscheman, Henk, Giltay, Erik J, Megens, Jos A J et al. (2011) A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. European journal of endocrinology 164(4): 635–42	Excluded on population – although some participants started gender-affirming hormones when young, the study does not report the proportion who started treatment when 18 years or less. Mean ages at start of treatment were 31.4 years (transfemales) and 26.1 years (transmales), suggesting the majority of participants were older than 18 years at the start of treatment. Outcomes not reported separately for people aged 18 years or less.
Author not, found (2014) Hormone therapy for the treatment of gender dysphoria. Lansdale, PA: HAYES, Inc	Full text paper not available.
Baba, T., Endo, T., Honnma, H. et al. (2007) Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduction 22(4): 1011–1016	Excluded on population – although study included some younger people (age range 17 to 47), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becerra-Fernandez A, Perez-Lopez G, Roman MM et al. (2014) Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. Endocrinologia y Nutricion: Organo de la Sociedad Espanola de Endocrinologia y Nutricion 61(7): 351–8	Excluded on population – although study included some younger people (age range 18 to 45), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becker I, Auer M, Barkmann C et al. (2018) A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Archives of Sexual Behavior 47(8): 2335–2347	Excluded on population – study included people aged 14 to 21 years. Outcomes not reported separately for people aged 18 years or less. Better evidence available – only 11 participants received gender-affirming hormones. The majority of the study cohort were either pre-treatment, received puberty suppression alone, or received hormones and underwent surgery.
Chew D, Anderson J, Williams K et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4): e20173742	Excluded on better available evidence - systematic review did not meta-analyse results from. Individual studies from this systematic review are either

Study reference	Reason for exclusion
	included, or excluded because they did not meet the PICO criteria.
Connolly MD, Zervos MJ, Barone CJ 2nd et al. (2016) The Mental Health of Transgender Youth: Advances in Understanding. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 59(5): 489–495	Excluded on intervention - review did not investigate gender-affirming hormones
de Vries ALC, McGuire JK, Steensma TD et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696–704	Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported. Outcomes reported in other study (with a population that more closely matches PICO)
Elamin MB, Garcia MZ, Murad MH et al. (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clinical Endocrinology 72(1): 1–10	Exclude on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Fernandez JD and Tannock LR (2016) Metabolic effects of hormone therapy in transgender patients. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(4): 383–8	Excluded on population – adult study, participants not 18 years or less (mean ages 31 and 27 years).
Fighera TM, Ziegelmann PK, Da Silva TR et al. (2019) Bone mass effects of cross-sex hormone therapy in transgender people: Updated systematic review and meta-analysis. Journal of the Endocrine Society 3(5): 943–964	Excluded on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Getahun D, Nash R, Flanders WD et al. (2018) Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Annals of Internal Medicine 169(4): 205–213	Excluded on population – adult study, participants not 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, de Antonio IE et al. (2014) Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation 23(2): 669–76	Excluded on population – although study included some younger people (age range 16 to 67), most participants were adults (mean age 31.2 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, Esteva I et al. (2012) Hormone-treated transsexuals report less	Excluded on population – adult study, participants not 18 years or less (mean age 24.6 years).

Study reference	Reason for exclusion
social distress, anxiety and depression. Psychoneuroendocrinology 37(5): 662–70	
Gooren LJ, van Trotsenburg MAA, Giltay EJ et al. (2013) Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. The Journal of Sexual Medicine 10(12): 3129–34	Excluded on population – study reports on cancer rates in people aged 18-80 years. The 3 cases of cancer all started gender-affirming hormone treatment >18 years.
Grimstad FW, Boskey E, Grey M (2020) New-Onset Abdominopelvic Pain After Initiation of Testosterone Therapy Among TransMasculine Persons: A Community-Based Exploratory Survey. LGBT health 7(5): Published Online:13 Jul 2020https://doi.org/10.1089/lgbt.2019.0258	Excluded on population – adult study, participants not 18 years or less.
Hannema SE, Schagen SEE, Cohen-Kettenis PT et al. (2017) Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. The Journal of Clinical Endocrinology and Metabolism 102(7): 2356–2363	Excluded on better evidence available – small study (n=28) with high drop-out rate (n=16 at final follow-up). Same outcomes reported in larger studies.
Jarin J, Pine-Twaddell E, Trotman G et al. (2017) Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 139(5)	Excluded on population and better evidence available. Although the study included some younger people (age range 13 to 25; mean age 16 and 18), the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. Outcomes were limited to physiological results (including haemoglobin, lipids and BMI). Follow-up only 6 months, other included studies report same outcomes with longer follow-up (12 to 31 months).
Keo-Meier CL, Herman LI, Reisner SL et al. (2015) Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. Journal of consulting and clinical psychology 83(1): 143–56	Excluded on population – although study included some younger people (age range 18 to 54), most participants were adults (mean age 26.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Klaver M, de Mutsert R, Wiepjes CM et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The Journal of Sexual Medicine 15(2): 251–260	Excluded on outcomes – reported outcomes not included in PICO document. The risk of obesity with gender-affirmed hormones was reported in an included study.
McFarlane T, Zajac JD, Cheung AS (2018) Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clinical Endocrinology 89(6): 700-711	Exclude on population – all included studies conducted in adult population.

Study reference	Reason for exclusion
Meriggiola MC, Armillotta F, Costantino A et al. (2008) Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. The Journal of Sexual Medicine 5(10): 2442–53	Excluded on population – adult study, participants not 18 years or less.
Nota NM, Wiepjes CM, de Blok, CJM et al. (2018) The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain: A Journal of Neurology 141(7): 2047–2054	Excluded on population – adult study, participants not 18 years or less.
Oda H and Kinoshita T (2017) Efficacy of hormonal and mental treatments with MMPI in FtM individuals: Cross-sectional and longitudinal studies. BMC Psychiatry 17(1): 256	Excluded on population – although study included some younger people (age range 15 to 43), most participants were adults (mean age around 25.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Olson-Kennedy J, Okonta V, Clark LF et al. (2018) Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 62(4): 397–401	Excluded on population – although study included some younger people (age range 12 to 23; mean age 18 years). Outcomes not reported separately for people aged 18 years or less. Outcomes limited to physiological results (including haemoglobin, lipids, liver enzymes and BMI). Same outcomes reported in included studies that had a less indirect population and a longer follow-up.
Ott J, Kaufmann U, Bentz K et al. (2010) Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertility and sterility 93(4): 1267–72	Excluded on population – adult study, participants not 18 years or less.
Pakpoor J, Wotton CJ, Schmierer K et al. (2016) Gender identity disorders and multiple sclerosis risk: A national record-linkage study. Multiple sclerosis. Multiple Sclerosis Journal. 22(13): 1759–1762	Excluded on population – although study included some younger people, outcomes not reported separately for people aged 18 years or less. Also exclude for intervention – unclear if people received gender-affirming hormones.
Pyra M, Casimiro I, Rusie L et al. (2020) An Observational Study of Hypertension and Thromboembolism among Transgender Patients Using Gender-Affirming Hormone Therapy. Transgender Health 5(1): 1–9	Excluded on population – adult study (age range 20-70). Age at which gender-affirming hormones started not reported.
Quiros C, Patrascioiu I, Mora M et al. (2015) Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion 62(5): 210–6	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
Rowniak S, Bolt L, Sharifi C (2019) Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. JBI Database of Systematic Reviews and Implementation Reports 17(9): 1826–1854	Exclude on population – all included studies conducted in adult population.
Sequeira GM, Kidd K, El Nokali NE et al. (2019) Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. Journal of Adolescent Health 65(6): 818–820	Exclude on outcome - study only reports BMI z-score over 12 month testosterone treatment. BMI not listed as an outcome of interest in the PICO document. Other included studies have investigated the impact of gender-affirming hormone treatment on CV risk profile, including longer term obesity rates, with a longer follow-up and more participants.
Shim JY, Laufer MR, Grimstad FW (2020) Dysmenorrhea and Endometriosis in Transgender Adolescents. Journal of Pediatric and Adolescent Gynecology. Available online 11 June 2020. https://doi.org/10.1016/j.jpag.2020.06.001	Exclude on population – only 2 participants taking testosterone before diagnosis of dysmenorrhea.
Slabbekoorn D, Van Goozen SHM, Gooren, LJG et al. (2001) Effects of cross-sex hormone treatment on emotionality in transsexuals. International Journal of Transgenderism 5(3): http://www.symposion.com/ijt/ijtvo05no03_02.htm	Excluded on population – adult study (age range 21 to 28 years)
Smith YLS., Van Goozen SHM, Kuiper AJ et al. (2005) Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. Psychological Medicine 35(1): 89–99	Excluded on population – results on adults only used to assess hormone treatment.
Sutherland N, Espinel W, Grotzke M et al. (2020) Unanswered Questions: Hereditary breast and gynecological cancer risk assessment in transgender adolescents and young adults. Journal of Genetic Counseling 29(4): 625–633	Excluded on study type – narrative review of 3 case reports.
van Velzen DM, Paldino A, Klaver M et al. (2019) Cardiometabolic Effects of Testosterone in Transmen and Estrogen Plus Cyproterone Acetate in Transwomen. The Journal of Clinical Endocrinology and Metabolism 104(6): 1937–1947	Excluded on population – adult study, participants not 18 years or less.
White Hughto JM and Reisner SL (2016) A Systematic Review of the Effects of Hormone Therapy on Psychological Functioning and Quality of Life in Transgender Individuals. Transgender Health 1(1): 21–31	Exclude on population – all included studies conducted in adult population.
Wiepjes CM, de Blok CJM, Staphorsius AS et al. (2020) Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study. Journal of Bone and Mineral Research 35(1): 64–70	Excluded on population – adult study, all participants started gender-affirming hormones after 18 years.
Wierckx K, Mueller S, Weyers S et al. (2012) Long-term evaluation of cross-sex hormone treatment in	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
transsexual persons. The Journal of Sexual Medicine 9(10): 2641–51	
Wierckx K, Van Caenegem E, Schreiner T et al. (2014) Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. The journal of sexual medicine 11(8): 1999–2011	Excluded on population – adult study, participants not 18 years or less.
Wilson R, Jenkins C, Miller H et al. (2006) The effect of oestrogen on cytokine and antioxidant levels in male to female transsexual patients. Maturitas 55(1): 14–8	Excluded on population – adult study, participants not 18 years or less.
Witcomb GL, Bouman WP, Claes L et al. (2018) Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. Journal of Affective Disorders 235: 308–315	Excluded on population – although study included some younger people (age range 15 to 79), most participants were adults (mean age around 30.4 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8 **Study location** Single centre, New York, United States **Study type** Prospective longitudinal study **Study aim** To assess the psychological wellbeing and quality of life in children and adolescents who have sought endocrine	Inclusion and exclusion not reported- it appears from the description in the publication that all people referred for gender dysphoria were invited to participate, and the vast majority agreed. Of the 95 treatment naïve people who entered the study, 50 people completed all follow-up questionnaires and were included in the analysis. No description of the 45 people without follow-up data reported. The study included 50 children, adolescents and young adults with gender dysphoria.	**Intervention** Endocrine interventions (the collective term used by authors for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for	**Critical Outcomes** ***Impact on mental health*** Depression symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R). Statistically significant improvements in CESD-R score were observed from baseline (initial assessment; 21.4 points) to about 12 months follow-up (13.9 points; p<0.001). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.27) and transmales (p=0.43). The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) was also used to assess depression symptoms. Depression scores improved from baseline (p< 0.001; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.07) and transmales (p=0.67). Suicidal ideation measured using the additional questions from the PHQ 9_Modified for Teens, was presented in 10% (5/50) of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no **Domain 2: Comparability** 1. c) no comparator **Domain 3: Outcome** 1. c) self-report 2. a) yes – 6 monthly assessment up to 12 months (preliminary results from an ongoing study) 3. c) Follow up rate less than 80% and no description of those lost **Overall quality is assessed as poor** Other comments: Although regression analysis results for some outcomes were controlled for use of medicines for mental health problems,

intervention to help with gender dysphoria. **Study dates** Study recruitment ran from December 2013 to December 2018; study is ongoing	17 transfemales and 33 transmales. Diagnostic criteria for gender dysphoria not reported. Mean age at baseline was 16.2 years (SD 2.2). Mean age at the start of gender-affirming hormone treatment not reported.	Transgender Health (WPATH) guidelines. Puberty suppression was: • GnRH agonist and/or anti-androgens (transfemales) • GnRH agonist or medroxyprogesterone (transmales) Average duration of GnRH analogue treatment not reported. Once eligible, gender-affirming hormones were offered, these were: • Oestradiol (transfemales) • Testosterone (transmales) Doses and route of administration not reported. After about 12-months treatment ('wave 3' in the study): • 24 people (48%) were on gender-affirming hormones alone • 12 people (24%) were on puberty suppression alone	participants at baseline and 6% (3/50) at about 12-month follow-up, no statistical analysis reported. The study also reported results by gender: In transfemales, 11.8% (2/17) had suicidal ideation at baseline compared with 5.9% (1/17) at 12-month follow-up (no statistically analysis reported) In transmales, 9.1% (3/33) had suicidal ideation at baseline compared with 6.1% (2/33) at 12-month follow-up (no statistically analysis reported) ***Impact on quality of life*** Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) scores: there was no statistically significant change in score from baseline to about 12-months (p=0.085; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found not statistically significant change from baseline in transfemales (p=0.06) and transmales (p=0.08). *No other critical or important outcomes reported*	details of these is not reported. Other co-morbidities not reported. Source of funding: None

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
		• 11 people (22%) were on both gender-affirming hormones and puberty suppression • 3 people (6%) were on no endocrine intervention Results not represented separately for the sub-group of people who received gender-affirming hormones. Average duration of treatment with gender-affirming hormones not reported. **Comparison** No comparison group. Change overtime reported.		

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Allen, LR, Watson, LB, Egan, AM et al. (2019) Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric	The study included adolescents and young adults (age range 13-20 years) who received services for gender dysphoria in a clinic in the United States. Participants were required to have received gender-	39 participants received gender-affirming hormones only 8 participants received a GnRH analogue followed by gender-affirming hormones.	**Critical Outcomes** ***Impact on mental health*** The Ask Suicide-Screening Questions (ASQ) instrument was used to assess suicidality. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean ASQ score was statistically significantly lower (from 1.11 [standard error	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Psychology 7(3): 302-311 **Study location** Single centre, Kansas City, United States **Study type** Retrospective longitudinal study **Study aim** To examine suicidality and general well-being following administration of gender-affirming hormones. **Study dates** Participants first presented to the clinic between 2015 and 2018.	affirming hormones for at least 3 months, and have pre-test and final assessment data points. No exclusion criteria reported. In total 47 adolescents and young adults with gender dysphoria were included: 14 transfemales (sex assigned at birth male) and 33 transmales (sex assigned at birth female). Diagnostic criteria for gender dysphoria not reported. Mean age at pre-test (before administration of gender-affirming hormones) was 16.59 years (range 13.73 to 19.04). Mean age at the start of treatment in the sub-group who received gender-affirming hormones-only was 16.72 years. Mean age at the start of treatment with gender-affirming hormones in people who previously	Mean duration of treatment in the gender-affirming hormones only subgroup was 366 days. Mean duration of gender-affirming hormone treatment in people who had previously received a GnRH analogue was not reported. Mean duration of treatment with a GnRH analogue was not reported. Participants were assessed at the start of treatment and at least 3 months after treatment.	(SE) 0.22] at baseline to 0.27 [SE 0.12] at final assessment; p<0.001). The authors also reported change in ASQ separately for transfemales (from 1.21 [SE 0.36] at baseline to 0.24 [SE 0.19] at final assessment) and transmales (from 1.01 [SE 0.36] at baseline to 0.29 [0.13] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales (p=0.79) ***Impact on quality of life*** Assessed using the General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory. Following an average of about 12 months treatment with gender-affirming hormones, adjusted mean GWBS score was statistically significantly higher (from 61.7 [SE 2.43] at baseline to 70.23 [2.15] at final assessment; p<0.002). The authors also reported change in GWBS of the Pediatric Quality of Life Inventory for transfemales (from 58.44 [SE 4.09] at baseline to 69.52 [SE 3.62] at final assessment) and transmales (from 64.95 [SE 2.66] at baseline to 70.94 [2.35] at final assessment). There was no statistically significant difference in change from baseline between transfemales and transmales (p=0.32) *No other critical or important outcomes reported*	3. a) secure record 4. b) no **Domain 2: Comparability** 2. c) no comparator **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of treatment was 366 days 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	received a GnRH analogue was not reported.			

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Kaltiala, R., Heino, E., Tyolajarvi, M. et al. (2020) Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nordic Journal of Psychiatry 74(3): 213-219 **Study location** Single centre, Tampere, Finland **Study type** Retrospective chart review **Study aim** To evaluate the psychosocial functioning and need for mental health treatment during the gender identity diagnostic phase and after about	The study included adolescents who were referred to the gender identity service before they 18 years old, were diagnosed with gender dysphoria, received gender-affirming hormones and completed a follow-up of approximately 12 months after starting hormones. In total 52 adolescents were included, comprising of 11 transfemales and 41 transmales. Gender dysphoria was diagnosed according to International Classification of Disease 10 (ICD-10). The authors state that the corresponding diagnosis to 'gender dysphoria' in	Intervention referred to as 'hormonal sex reassignment treatment' – details of intervention not reported, although gender-affirming hormones were prescribed to all participants. It is not clear from the study whether additional interventions were prescribed. Medical records reviewed for the 'real-life phase' – the approximately 12 months follow-up period for this population in Finland.	**Critical Outcomes** ***Impact on mental health*** Of the 52 people who received gender-affirming hormones, 50% (26/52) needed mental health treatment before or during the assessment and 46% (24/51) needed mental health treatment during the 12-month 'real life' phase (no statistically significant difference). For specific symptoms / conditions: • depression: 54% (28/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001) • anxiety: 48% (25/52) needed treatment before or during the assessment and 15% (8/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001) • suicidality/self-harm: 35% (18/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (statistically significant reduction, p<0.001) • conduct problems/antisocial: 14% (7/52) needed treatment before or during the	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – 12 month follow-up 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
a year on gender-affirming hormones. **Study dates** 2011 to 2017	the ICD-10 is 'transsexualism'. Mean age at diagnosis 18.1 years (range 15.2 to 19.9)		assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.18) • psychotic symptoms/psychosis: 2% (1/52) needed treatment before or during the assessment and 4% (2/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.56) • substance abuse: 4% (2/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.56) • autism: 12% (6/52) needed treatment before or during the assessment and 6% (3/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.30) • ADHD: 10% (5/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 0.09) • eating disorder: 2% (1/52) needed treatment before or during the assessment and 2% (1/52) needed treatment during the 12-month 'real life' phase (no statistically significant difference, p= 1.0). No details of actual treatment reported. **Important Outcomes** ***Psychosocial Impact*** Study reported on measures of functioning in different domains of adolescent development,	Other comments: None Source of funding: No source of funding reported

			reported over the approximately 12-month period after starting gender-affirming hormones (referred to as the 'real-life phase' in Finland) Significantly fewer participants were living with parent(s)/ guardians during the real-life phase (40%; 21/50) compared with during gender identity assessment (73%; 38/52; p=0.001)) There was a statistically significant reduction in the number of participants with normative peer contacts, from gender identity assessment (89%; 46/52) to the real-life phase (81%; 42/52; p<0.001). There was no significant difference in the number of participants who were progressing normally in school or work during gender identity assessment (64%; 33/52) compared with the real-life phase (60%; 31/52). There was no significant difference in the number of participants who have been dating or were in steady relationships during gender identity assessment (62%; 32/50) compared with the real-life phase (58%; 30/52). There was no significant difference in the number of participants who were able to deal with matters outside of the home in an age-appropriate manner during gender identity assessment (81% (42/52) compared with the real-life phase (81%; 42/52)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			No other critical or important outcomes reported	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

Full citation
Khatchadourian K, Amed S, Metzger DL (2014) Clinical management of youth with gender dysphoria in Vancouver. The Journal of pediatrics 164(4): 906-11
 	
Study location
Single centre study, Vancouver, Canada
 	
Study type
Retrospective chart review
 	
Study aim
To describe the patient characteristics, clinical management, and response to treatment in a cohort of people seen in a single clinic.
 	
Study dates
1998 to 2011
	Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.
	
	63 children, adolescents and young people with gender dysphoria who started gender-affirming hormones, out of 84 young people seen in the unit between 1998 and 2011.
	39 transfemales and 24 transmales.
	
	Diagnostic criteria for gender dysphoria not reported.
	
	Mean age at the start of gender-affirming hormone treatment was 17.4 years (SD 1.9).
		Intervention
		Transfemales: Oestrogen (oral micronized 17β-oestradiol)
		Transmales: Testosterone (injectable testosterone enanthate and/or cypionate)
		
		19 participants (30%) had previously received a GnRH analogue. The median time from start of GnRH analogue to start of gender-affirming hormones was 11.3 months (range 2.2 to 42.0). 11 participants continued GnRH analogues after starting gender-affirming hormones.
		
		Average duration of treatment with a GnRH analogue not reported
		
		Comparison
		No comparator
			Critical Outcomes
			
			No critical outcomes assessed.
			
			Important outcomes
			
			Safety
			Of the 63 participants who received gender-affirming hormones:
			• No participants permanently discontinued gender-affirming hormones
			• 3 participants (5%) temporarily discontinued treatment:
			  ○ 2 transmales due to concomitant mental health comorbidities
			  ○ 1 transmale due to androgenic alopecia.
			  ○ No transfemale stopped treatment.
			The authors report that all patients eventually restarted gender-affirming hormones, although they do not report how long treatment was
				This study was appraised using the Newcastle-Ottawa tool for cohort studies.
				
				Domain 1: Selection domain
				1. b) somewhat representative
				2. c) no-non exposed cohort
				3. a) secure record*
				4. b) no
				Domain 2: Comparability
				1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders
				Domain 3: Outcome
				1. b) record linkage
				2. b) no – although follow-up time is reported for patients with more than 1 clinic visit, duration of treatment with gender-affirming hormones is not reported
				3. c) incomplete - missing data
				
				Overall quality is assessed as poor

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			stopped for, or what the effect of stopped treatment was. • No participants reported major complications • 12 participants (19%) had minor complications: ○ 7 transmales had severe acne (requiring isotretinoin) ○ 1 transmale had andogenic alopecia ○ 3 transmales had mild dyslipidaemia (levels not reported) ○ 1 transmale had significant mood swings ○ No transfemales had minor complications	Other comments: Mental health comorbidity was reported for all participants but not for the gender-affirming hormone cohort separately. Concomitant use of other medicines was not reported. Source of funding: No source of funding identified.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klaver, Maartje, de Mutsert, Renee, van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3) **Study location** Single centre, Amsterdam, Netherlands	Participants were included if i) they had started GnRH analogue treatment before 18 years, ii) if whole body dual-energy radiograph absorptiometry was performed at least once during treatment (4 months before or after the start of GnRH analogues or gender-affirming hormones, or	Transfemales: Oestrogen (17-β oestradiol [E2]) orally, starting with 5 mcg/kg body weight per day, which was increased every 6 months until the maintenance dose of 2 mg per day was reached. Transmales: mixed testosterone esters (Sustanon), 25 mg/m^2 body surface area every 2 weeks intramuscularly,	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Safety*** Safety outcomes reported separately for transfemales and transmales. **For transfemales**, from the start of gender-affirming hormone treatment to age 22 years: • Mean BMI statistically significantly increased (mean change +1.9, 95% CI 0.6 to 3.2, p<0.005; mean BMI at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Study type Retrospective chart review **Study aim** To examine the effects of treatment on changes in cardiovascular risk factors, including BMI, blood pressure, insulin sensitivity, and lipid levels. **Study dates** 1998-2015	within 1.5 years before or after the 22nd birthday), iii) if they were likely to have had at least 1 medical consultation in young adulthood. The study included 192 young people with dysphoria who met the above inclusion criteria: 71 transfemales and 121 transmales. Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Mean age at the start of gender-affirming hormones was 16.4 years (SD 1.1) for transfemales and 16.9 years (SD 0.9) for transmales.	increased every 6 months to maintenance dose of 250 mg every 3 to 4 weeks. When GnRH analogues were started after the age of 16 years a different hormone starter dose was used (1 mg oestrogen daily and 75 mg testosterone weekly). Median (IQR) duration of GnRH analogue (monotherapy) was 2.1 years (1.0 to 2.7) in transfemales and 1.0 (0.5 to 2.9) for transmales.	22 years= 23.2, 95% CI 21.6 to 24.8). At age 22 years, 9.9% of the cohort were obese, compared with 3.0% in reference cisgender population[1]. • Mean systolic blood pressure (SBP) did not significantly change (mean change -3 mmHg, 95% CI -8 to 2; mean SBP at 22 years= 117 mmHg, 95% CI 113 to 122) • Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 3 to 10, p<0.001; mean DBP at 22 years= 75 mmHg, 95% CI 72 to 78) • Mean glucose level did not significantly change (mean change +0.1 mmol/L, 95% CI -0.1 to 0.2; mean glucose level at 22 years= 5.0 mmol/L, 95% CI 4.8 to 5.1) • Mean insulin level did not significantly change (mean change +2.7 mU/L, 95% CI -1.7 to 7.1; mean insulin level at 22 years= 5.0 mU/L (4.8 to 5.1) • Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) did not significantly change (mean change +0.7, 95% CI -0.2 to 1.5; mean HOMA-IR at 22 years 2.9, 95% CI 1.9 to 3.9) • Mean total cholesterol did not significantly change (mean change +0.1 mmol/L, 95% CI -0.2 to 0.4; mean total cholesterol at 22 years 4.1 mmol/L, 95% CI 3.8 to 4.4) • Mean HDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95% CI -0.1 to 0.2; mean HDL cholesterol at 22 years 1.6 mmol/L, 95% CI 1.4 to 1.7) • Mean LDL cholesterol did not significantly change (mean change +0.0 mmol/L, 95%	of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes- follow-up from start of gender-affirming hormones to age 22 years, around 5 years 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: No external funding

			CI -0.3 to 0.2; mean LDL cholesterol at 22 years 2.0 mmol/L, 95% CI 1.8 to 2.3) • Mean triglycerides statistically significantly increased (mean change +0.2 mmol/L, 95% CI 0.0 to 0.5, p<0.05; triglyceride level at 22 years 1.1 mmol/L, 95% CI 0.9 to 1.4) **For transmales**, from the start of gender-affirming hormone treatment to age 22 years: • Mean BMI statistically significantly increased (mean change +1.4, 95% CI 0.8 to 2.0, p<0.005; mean BMI at 22 years= 23.9, 95% CI 23.0 to 24.7). At age 22 years, 6.6% of the cohort were obese, compared with 2.2% in reference cisgender population[1]. • Mean systolic blood pressure (SBP) statistically significantly increased (mean change +5 mmHg, 95% CI 1 to 9; mean SBP at 22 years= 126 mmHg, 95% CI 122 to 130) • Mean diastolic blood pressure (DBP) statistically significantly increased (mean change +6 mmHg, 95% CI 4 to 9, p<0.001; mean DBP at 22 years= 74 mmHg, 95% CI 72 to 77) • Mean glucose level did not significantly change (mean change 0.0 mmol/L, 95% CI -0.2 to 0.2; mean glucose level at 22 years= 4.8 mmol/L, 95% CI 4.7 to 5.0) • Mean insulin level statistically significantly decreased (mean change -2.1 mU/L, 95% CI -3.9 to -0.3, p<0.05; mean insulin level at 22 years= 8.6 mU/L (6.9 to 10.2) • Insulin resistance (mean Homeostatic Model Assessment of Insulin Resistance [HOMA-IR]) statistically significantly	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			decreased (mean change -0.5, 95% CI -1.0 to -0.1, p<0.05; mean HOMA-IR at 22 years 1.8, 95% CI 1.4 to 2.2) • Mean total cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, p<0.001; mean total cholesterol at 22 years 4.6 mmol/L, 95% CI 4.3 to 4.8) • Mean HDL cholesterol statistically significantly decreased (mean change -0.3 mmol/L, 95% CI -0.4 to -0.2, p<0.001; mean HDL cholesterol at 22 years 1.3 mmol/L, 95% CI 1.2 to 1.3) • Mean LDL cholesterol statistically significantly increased (mean change +0.4 mmol/L, 95% CI 0.2 to 0.6, p<0.001; mean LDL cholesterol at 22 years 2.6 mmol/L, 95% CI 2.4 to 2.8) • Mean triglycerides statistically significantly increased (mean change +0.5 mmol/L, 95% CI 0.3 to 0.7, p<0.001; triglyceride level at 22 years 1.3 mmol/L, 95% CI 1.1 to 1.5)	

[1] Reference population taken from Fredriks et al. (2000)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of Clinical Endocrinology and Metabolism 100(2): e270-5 **Study location** Single centre, Amsterdam, Netherlands **Study type** Retrospective longitudinal study **Study aim** To assess peak bone mass in young adults with gender dysphoria who had received GnRH analogues and gender-affirming hormones during their pubertal years. **Study dates**	34 young people with gender dysphoria who received GnRH analogues, gender-affirming hormones and gonadectomy. The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively. Participants were required to meet the DSM-IV-TR criteria for gender identity disorder of adolescence. Participants were included if they had undergone gonadectomy between June 1998 and August 2012, and they were at least 21 years old when they had the surgery. Bone mineral density data were also required at the start of GnRH analogue, gender-affirming hormones and at the age of 22 years. No concomitant treatments were reported.	**Intervention** Transfemales - oral 17-β oestradiol (incremental dosing) Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing) Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8). The GnRH analogue was SC triptorelin 3.75 mg every 4 weeks. No details of gonadectomy reported. **Comparison** No comparison group. Comparison over time reported.	**Critical outcomes** No critical outcomes reported **Important outcomes** **Safety** ***Bone density: lumbar spine*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.22 (0.02) • Age 22 years: 0.23 (0.03) • p=0.003 z-score (range) • Start of gender-affirming hormones: -0.90 (0.80) • Age 22 years: -0.78 (1.03) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.24 (0.02) • Age 22 years: 0.25 (0.28 • p=0.001 z-score (SD) • Start of gender-affirming hormones: -0.50 (0.81) • Age 22 years: -0.033 (0.95) • p=0.002	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. 3. c) follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor** Other comments: Within person comparison. Small numbers of participants in each subgroup. No

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Gonadectomy took place between June 1998 and August 2012	At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11). In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0).		**Lumbar spine bone mineral density (BMD)** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.84 (0.11) • Age 22 years: 0.93 (0.10) • p<0.001 z-score (range) • Start of gender-affirming hormones: -1.01 (0.98) • Age 22 years: -1.36 (0.83) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.91 (0.10) • Age 22 years: 0.99 (0.13) • P<0.001 z-score (range) • Start of gender-affirming hormones: -0.72 (0.99) • Age 22 years: -0.33 (1.12) • No statistically significant difference ***Bone density: femoral region, nondominant side*** **Femoral region, nondominant side BMAD** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.26 (0.04) • Age 22 years: 0.28 (0.05)	concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• No statistically significant difference z-score (SD) • Start of gender-affirming hormones: -1.57 (1.74) • Age 22 years: Not reported • No statistical analysis reported Change from starting gender-affirming hormones to age 22 years in transmales- Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.31 (0.04) • Age 22 years: 0.33 (0.05) • p=0.010 z-score (SD) • Start of gender-affirming hormones: -0.28 (0.74) • Age 22 years: Not reported • No statistical analysis reported **Femoral region, nondominant side BMD** Change from starting gender-affirming hormones to age 22 years in transfemales- Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.87 (0.08) • Age 22 years: 0.94 (0.11) • P=0.009 z-score (SD) • Start of gender-affirming hormones: -0.95 (0.63) • Age 22 years: -0.69 (0.74) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales- Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.88 (0.09) • Age 22 years: 0.95 (0.10)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• P<0.001 z-score (SD) • Start of gender-affirming hormones: -0.35 (0.79) • Age 22 years: -0.35 (0.74) • p=0.006	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Kuper, Laura E, Stewart, Sunita, Preston, Stephanie et al. (2020) Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 145(4) **Study location** Single centre, Texas, USA **Study type** Prospective longitudinal study **Study aim** To: • explore how baseline body dissatisfaction, depression, and anxiety symptoms vary by gender,	148 children and adolescents with gender dysphoria, n=148, of whom: • 25 received puberty suppression only • 93 received gender-affirming hormone therapy only • 30 received both Results for treatments reported separately. Mean age at initial assessment was 15.4 years (range 9 to 18). Mean age at start of gender-affirming hormone therapy was 16.2 years (range 13.2 to 18.6). All participants met the Diagnostic and Statistical	Hormone therapy, guided by Endocrine Society Clinical Practice Guidelines Follow-up at least 18 months from initial assessment at the clinic. Mean duration of gender-affirming hormone therapy before follow-up was 10.9 months (range 1 to 18; SD 3.3)	**Critical Outcomes** ***Impact on mental health*** Mean depression score, assessed using the Quick Inventory of Depressive Symptoms (QIDS), self-reported was 9.6 (SD 5.0) at baseline and 7.4 (SD 4.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean depression score, assessed using the QIDS, clinician-reported was 5.9 (SD 4.1) at baseline and 6.0 (SD 3.8) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean anxiety score, assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire was 32.6 (SD 16.3) at baseline and 28.4 (SD 15.9) at	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. d) assessors not blinded to treatment 2. a) yes – follow-up at least 18 months from initial assessment. Mean duration of gender-affirming hormone

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
age at initial assessment, and Tanner stage at first medical visit • examine how body dissatisfaction, depression, and anxiety symptoms change over the first year of gender-affirming hormone treatment • explore how any changes vary by affirmed gender, Tanner stage, age, type of treatment, months on gender-affirming hormone therapy, mental health treatment received, and whether chest surgery was also obtained (among transmales). **Study dates** Initial participant assessments took place between August 2014 and March 2018.	Manual of Mental Disorders, Fifth Edition criteria for gender dysphoria. Specific inclusion and exclusion criteria for the study are not reported. It would appear that all children and adolescents eligible for gender-affirming hormones were considered eligible for the study. The authors state that before initial assessment with a psychologist, psychiatrist, and/or clinical therapist, parents completed a phone intake survey. Around one-third of families did not follow-up after the phone intake.		follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean panic score, assessed using specific questions from the SCARED questionnaire was 8.1 (SD 6.3) at baseline and 7.1 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean generalised anxiety score, assessed using specific questions from the SCARED questionnaire was 10.0 (SD 5.1) at baseline and 8.8 (SD 6.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean social anxiety score, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.1) at baseline and 7.7 (SD 4.2) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean separation anxiety score, assessed using specific questions from the SCARED	treatment was 10.9 months. 3. c) patient numbers vary by outcome with no explanation **Overall quality is assessed as poor** Other comments: None Source of funding: Supported by Children's Health. The Research Electronic Data Capture database was funded by the Clinical and Translational Science Awards program

			questionnaire was 3.5 (SD 3.0) at baseline and 3.1 (SD 2.5) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. Mean school avoidance score, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming hormones and it is unclear whether the change in score was statistically significant. The authors also reported results separately for transfemales and transmales: **Transfemales** No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant. • Mean depression symptoms, assessed using the QIDS, self-reported was 7.5 (SD 4.9) at baseline and 6.6 (SD 4.4) at follow-up. • Mean depression symptoms, assessed using the QIDS, clinician-reported was 4.2 (SD 3.2) at baseline and 5.4 (SD 3.4) at follow-up. • Mean anxiety symptoms, assessed using the SCARED questionnaire was 26.4 (SD 14.2) at baseline and 24.3 (SD 15.4) at follow-up.	

			• Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 5.7 (SD 4.9) at baseline and 5.1 (SD 4.9) at follow-up. • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.6 (SD 5.1) at baseline and 8.0 (SD 5.1) at follow-up. • Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 7.1 (SD 3.9) at baseline and 6.8 (SD 4.4) at follow-up. • Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 3.4 (SD 3.3) at baseline and 2.7 (SD 2.3) at follow-up. • Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 1.8 (SD 1.7) at baseline and 1.9 (SD 2.1) at follow-up. **Transmales** No statistical analyses were reported for this sub-group and it is unclear whether any changes in score were statistically significant. • Mean depression symptoms, assessed using the QIDS, self-reported was 10.4 (SD 5.0) at baseline and 7.5 (SD 4.5) at follow-up. • Mean depression symptoms, assessed using the QIDS, clinician-reported was 6.7 (SD 4.4) at baseline and 6.2 (SD 4.1) at follow-up. • Mean anxiety symptoms, assessed using the SCARED questionnaire was 35.4 (SD	

			16.5) at baseline and 29.8 (SD 15.5) at follow-up. • Mean panic symptoms, assessed using specific questions from the SCARED questionnaire was 9.3 (SD 6.5) at baseline and 7.9 (SD 6.5) at follow-up. • Mean generalised anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 10.4 (SD 5.0) at baseline and 9.0 (SD 5.1) at follow-up. • Mean social anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 8.5 (SD 4.0) at baseline and 7.8 (SD 4.1) at follow-up. • Mean separation anxiety symptoms, assessed using specific questions from the SCARED questionnaire was 4.2 (SD 3.4) at baseline and 3.4 (SD 2.6) at follow-up. • Mean school avoidance symptoms, assessed using specific questions from the SCARED questionnaire was 2.6 (SD 2.1) at baseline and 2.0 (SD 2.0) at follow-up. No difference in impact on mental health found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint. **Important Outcomes** ***Impact on body image***	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Mean Body Image Scale (BIS) score was 70.7 (SD 15.2) at baseline and 51.4 (SD 18.3) at follow-up. The authors do not present statistical analysis for this population and it is unclear whether the change in score was statistically significant. The authors also reported body image results separately for transfemales and transmales. No statistical analyses were reported for this sub-groups and it is unclear whether changes in score were statistically significant. • In transfemales, BIS score was 67.5 (SD 19.5) at baseline and 49.0 (SD 21.6) at follow-up. • In transmales, BIS score was 71.1 (SD 13.4) at baseline and 52.9 (SD 16.8) at follow-up. No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint. *No other critical or important outcomes reported*	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Study dates Lopez de Lara, D., Perez Rodriguez, O., Cuellar Flores, I. et al. (2020) Psychosocial assessment in transgender adolescents. Anales de Pediatria **Study location** Single centre in Madrid, Spain **Study type** Prospective analytical study **Study aim** To assess the psychosocial status of patients seeking care in the paediatric endocrinology clinic for gender dysphoria, and the impact on psychosocial status of gender-affirming hormone therapy at 12 months of treatment **Study dates** Not reported	23 adolescents with gender dysphoria; 16 transmale and 7 transfemale. Participants were required to be at a stage of pubertal development of Tanner 2 or higher. People with mental health comorbidity that could affect the experience of gender dysphoria were excluded. Mean age at baseline was 16 years (range 14 to 18). 30 cisgender controls, matched for age, ethnicity, and socioeconomic status	Gender-affirming hormones- • Oral oestradiol • Intramuscular testosterone Participants had previously received gonadotropin-releasing hormone (GnRH) analogues in the intermediate pubertal stages (Tanner 2---3).	**Critical Outcomes** ***Impact on gender dysphoria*** Following gender-affirming hormones for 12 months, mean (±SD) Utrecht Gender Dysphoria Scale (UGDS) score statistically significantly improved, from 57.1 (±4.1) at baseline to 14.7 (±3.2; p<0.001) ***Impact on mental health*** Mean depression score statistically significantly improved following treatment with gender-affirming hormones. Mean Beck Depression Inventory II (BDI-II) score (±SD) reduced from 19.3 points (±5.5) at baseline to 9.7 points (±3.9) at 12 months (p<0.001). Mean anxiety scores statistically significantly improved following treatment with gender-affirming hormones. Mean (±SD) State-Trait Anxiety Inventory (STAI) State subscale score improved from 33.3 points (±9.1) at baseline to 16.8 points (±8.1) at 12 months (p<0.001). Mean (±SD) State-Trait Anxiety Inventory (STAI) Trait subscale score improved from 33.0 points (±7.2) at baseline to 18.5 points (±8.4) at 12 months (p<0.001). **Important Outcomes** ***Psychosocial Impact*** There was not change in family functioning, measured using the Family APGAR test, from baseline (17.9 points) to 1 year after starting	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria. 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. Not applicable – although a control group is reported on, people in this group did not have gender dysphoria. **Domain 3: Outcome** 1. d) assessors not blinded to treatment 2. a) yes – 12 months treatment with gender-affirming hormones 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			gender-affirming hormones (18.0 points; no statistical analysis reported). Results from the Strengths and Difficulties Questionnaire, Spanish Version (SDQ-Cas) showed statistically significant improvements from baseline (14.7 points; SD±3.3) to 12 months after gender-affirming hormones (10.3 points; SD±2.9; p<0.001) *No other critical or important outcomes reported*	Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Stoffers, Iris E; de Vries, Martine C; Hannema, Sabine E (2019) Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. The journal of sexual medicine 16(9): 1459-1468 **Study location** Single centre, Leiden, Netherlands **Study type** Retrospective chart review **Study aim** To report changes in height, BMI, blood pressure, laboratory parameters and bone density. **Study dates** November 2010 to August 2018	62 transmales with gender dysphoria. participants were required to have been receiving testosterone therapy for at least 6 months. Further inclusion or exclusion criteria not reported. Gender dysphoria was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria. .	Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 125 mg every 2 weeks or 250 mg every 3-4 weeks. A more rapid dose escalation was using in patients who started GnRH analogue treatment at 16 years or older. Median age at start of testosterone treatment was 17.2 years (range 14.9 to 18.4) Median duration of testosterone treatment was 12 months (range 5 to 33) Median duration of GnRH analogue treatment was 8 months (range 3 to 39)	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Safety*** ***Bone mineral density (BMD): lumbar spine*** There was no statistically significant difference in lumber spine bone mineral density (BMD) from start of testosterone treatment to any timepoint, up to 24 months follow-up. Mean (±SD), g/cm^2: • Start of testosterone: 0.90 (±0.11) • 6 months: 0.94 (±0.10) • 12 months: 0.95 (±0.09) • 24 months: 0.95 (±0.11) z-score (±SD): • Start of testosterone: -0.81 (±1.02) • 6 months: -0.67 (±0.95) • 12 months: -0.66 (±0.81) • 24 months: -0.74 (±1.17) ***Bone mineral density (BMD): femoral neck (hip)*** There was no statistically significant difference in right or left femoral neck (hip) bone mineral density (BMD) from start of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: None

			testosterone treatment to any timepoint, up to 24 months follow-up.
			Right
			Mean (±SD), g/cm^2:
			• Start of testosterone: 0.77 (±0.08)
			• 6 months: 0.84 (±0.11)
			• 12 months: 0.82 (±0.08)
			• 24 months: 0.85 (±0.11)
			z-score (±SD):
			• Start of testosterone: -0.97 (0.79)
			• 6 months: -0.54 (±0.96)
			• 12 months: -0.80 (±0.69)
			• 24 months: -0.31 (±0.84)
			Left
			Mean (±SD), g/cm^2:
			• Start of testosterone: 0.76 (±0.09)
			• 6 months: 0.83 (±0.12)
			• 12 months: 0.81 (±0.08)
			• 24 months: 0.86 (±0.09)
			z-score (±SD):
			• Start of testosterone: -1.07 (0.85)
			• 6 months: -0.62 (±1.12)
			• 12 months: -0.93 (±0.63)
			• 24 months: -0.20 (±0.70)
			
			Other safety-related outcomes
			• Alkaline phosphatase: statistically significant increases observed from start of testosterone treatment to 6 months and 12 months ($p<0.001$), although difference at 24 months was not statistically significant. Median (IQR), U/L
			  ○ Start of testosterone: 102 (78 to 136)
			  ○ 6 months: 115 (102 to 147)
			  ○ 12 months: 112 (88 to 143)
			  ○ 24 months: 81 (range 69 to 98)
			• Creatinine: statistically significant increases observed from start of	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			testosterone treatment to 6, 12 and 24 months (p<0.001). Mean (±SD), umol/L ○ Start of testosterone: 62 (±7) ○ 6 months: 70 (±9) ○ 12 months: 74 (±10) ○ 24 months: 81 (±10) There was no statistically significant change from start of testosterone treatment in: • HbA1c • Aspartate aminotransferase (AST) • Alanine aminotransferase (ALT) • Gamma-glutamyl transferase • Urea Numerical results, follow-up duration and further details of statistical analysis not reported.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Vlot MC, Klink DT, den Heijer M et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 **Study location** Single centre, Amsterdam, Netherlands **Study type** Retrospective chart review **Study aim** To investigate the impact of GnRH analogues and gender-affirming hormones on bone mineral apparent density (BMAD) in transgender adolescents. The study also report on levels of bone turnover markers, although the authors concluded that the	70 adolescents with gender dysphoria (42 transmales and 28 transfemales). Median age (range) at the start of gender-affirming hormones was 16.3 years (15.9 to 19.5) for transmales and 16.0 years (14.0 to 18.9) for transfemales. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who received GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales	Transfemales: Oestradiol oral Dose escalated every 6 months until standard adult dose of 2 mg daily was reached Transmales: Testosterone intramuscular injection (Sustanon 250 mg). Dose escalated every 6 months up to the standard adult dose of 250 mg every 4 weeks or 250 mg every 3-4 weeks. All participants previously received a GnRH analogue (triptorelin 3.75 mg subcutaneously every 4 weeks) Median duration of GnRH analogue therapy not reported.	**Critical outcomes** No critical outcomes reported **Important outcomes** ***Bone density: lumbar spine*** **Lumbar spine bone mineral apparent density (BMAD)** Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24) • 24-month follow-up (C24): 0.22 (0.19 to 0.27) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) • 24-month follow-up (C24): • Statistically significant increase (p≤0.05) Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.22 (0.19 to 0.24) • 24-months: 0.23 (0.21 to 0.26) • Statistically significant increase (p≤0.05) z-score (range) • Start of gender-affirming hormones: -1.15 (-2.21 to 0.08) • 24-months: -0.66 (-1.66 to 0.54)	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes- 24 month follow-up 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor.** Other comments: None Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
added value of these seems to be limited. **Study dates** Participants started gender-affirming therapy between 2001 and 2011	group had a bone age of <15 years and the old transfemales group ≥15 years.		Statistically significant increase (p≤0.05) Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.23 (0.19 to 0.28) • 24-months: 0.25 (0.22 to 0.28) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.84 (-2.2 to 0.87) • 24-months: -0.15 (-1.38 to 0.94) Statistically significant increase (p≤0.01) Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.24 (0.20 to 0.28) • 24-months: 0.25 (0.21 to 0.30) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.29 (-2.28 to 0.90) • 24-months: -0.06 (-1.75 to 1.61) Statistically significant increase (p≤0.01) ***Bone density: femoral neck*** **Femoral neck BMAD** Transfemales (bone age <15 years), change from starting gender-affirming hormones to 24 months follow-up.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Median (range), g/m^3 • Start of gender-affirming hormones: 0.27 (0.20 to 0.33) • 24-months: 0.27 (0.20 to 0.36) • No statistically significant change z-score (range) • Start of gender-affirming hormones: -1.32 (-3.39 to 0.21) • 24-months: -1.30 (-3.51 to 0.92) • No statistically significant change Transfemales (bone age ≥15 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.30 (0.26 to 0.34) • 24-months: 0.29 (0.24 to 0.38) • No statistically significant change z-score (range) • Start of gender-affirming hormones: -0.36 (-1.50 to 0.46) • 24-months: -0.56 (-2.17 to 1.29) • No statistically significant change Transmales (bone age <14 years), change from starting gender-affirming hormones to 24 months follow-up. Median (range), g/m^3 • Start of gender-affirming hormones: 0.30 (0.22 to 0.35) • 24-months: 0.33 (0.23 to 0.37) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.37 (-2.28 to 0.47) • 24-months: -0.37 (-2.03 to 0.85)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• Statistically significant increase (p≤0.01) Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up. • Start of gender-affirming hormones: 0.30 (0.23 to 0.41) • 24-months: 0.32 (0.23 to 0.41) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.27 ((-1.91 to 1.29) • 24-months: 0.02 (-2.1 to 1.35) • Statistically significant increase (p≤0.05)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
    a) Truly representative (one star)
    b) Somewhat representative (one star)
    c) Selected group
    d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
    a) Drawn from the same community as the exposed cohort (one star)
    b) Drawn from a different source
    c) No description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a) Secure record (e.g., surgical record) (one star)
    b) Structured interview (one star)
    c) Written self report
    d) No description
    e) Other
4) Demonstration that outcome of interest was not present at start of study
    a) Yes (one star)
    b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
    a) The study controls for age, sex and marital status (one star)
    b) Study controls for other factors (list) _____ (one star)
    c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
    a) Independent blind assessment (one star)
    b) Record linkage (one star)
    c) Self report
    d) No description
    e) Other
2) Was follow-up long enough for outcomes to occur
    a) Yes (one star)
    b) No
    Indicate the median duration of follow-up and a brief rationale for the assessment above:_____
3) Adequacy of follow-up of cohorts
    a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
c) Follow up rate less than 80% and no description of those lost
d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix G Grade profiles

Table 2: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? - Gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria (1 uncontrolled, prospective observational study)									
Change from baseline in mean gender dysphoria score, measured using the UGDS (duration of treatment 12 months). Higher scores indicate greater gender dysphoria.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 57.1 (SD 4.1) T1 (12 months) = 14.7 (SD 3.2) Statistically significant improvement, p<0.001	Critical	VERY LOW

Abbreviations: p: p-value; SD: standard deviation; UGDS: Utrecht Gender Dysphoria Scale

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. 2020 was assessed at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 3: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health (3 uncontrolled, prospective observational studies and 2 uncontrolled, retrospective observational studies)									
Change from baseline in mean depression score, measured using the BDI-II (duration of treatment 12 months). Higher scores indicate more severe depression.									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 19.3 (SD 5.5) T1 (12 months) = 9.7 (SD 3.9) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in mean depression score, measured using the CESD-R (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 21.4 Wave 3 (approx. 12 months) = 13.9 Statistically significant improvement (p<0.001)	Critical	VERY LOW
Change from baseline in depression score, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Statistically significant reductions in mean score, p<0.001 Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	Baseline = 9.6 (SD 5.0) Follow-up = 7.4 (SD 4.5) No statistical analysis reported for the sub-group of participants receiving gender-affirming hormones	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=106	None	Baseline = 5.9 (SD 4.1) Follow-up = 6.0 (SD 3.8)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Kuper et al. 2020							No statistical analysis reported for the sub-group of participants who received gender-affirming hormones		
Need for treatment due to depression, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 54% (28/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in anxiety score, measured using the STAI-State subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.3 (SD 9.1) T1 (12 months) = 16.8 (SD 8.1) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in anxiety score, measured using the STAI-Trait subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.0 (SD 7.2) T1 (12 months) = 18.5 (SD 8.4) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in anxiety symptoms, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 32.6 (SD 16.3) Follow-up = 28.4 (SD 15.9) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in panic symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.1 (SD 6.3) Follow-up = 7.1 (SD 6.5) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in generalised anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 10.0 (SD 5.1) Follow-up = 8.8 (SD 5.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in social anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.5 (SD 4.1) Follow-up = 7.7 (SD 4.2) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in separation anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=81	None	Baseline = 3.5 (SD 3.0) Follow-up = 3.1 (SD 2.5) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in school avoidance, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 2.6 (SD 2.1) Follow-up = 2.0 (SD 2.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Need for treatment due to anxiety, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 48% (25/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in adjusted mean suicidality score, measured using the ASQ instrument (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 1.11 (SE 0.22) T1 (final assessment) = 0.27 (SE 0.12) Statistically significant improvement in score from T0 to T1, p<0.001	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 10% (5/50) Wave 3 (approx. 12 months) = 6% (3/50)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							No statistical analysis reported		
Change from baseline in suicidal ideation (passive), information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness [6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 81% (105 people) 1 month before initial assessment = 25% (33 people) Follow-up period = 38% (51 people) No statistical analysis reported	Critical	VERY LOW
Change from baseline in suicide attempts, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness[6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 15% (20 people) 3 months before initial assessment = 2% (3 people) Follow-up period = 5% (6 people) No statistical analysis reported	Critical	VERY LOW
Change from baseline in non-suicidal self-injury, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness[6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 52% (68 people) 3 months before initial assessment = 10% (13 people) Follow-up period = 17% (23 people) No statistical analysis reported	Critical	VERY LOW
Need for treatment due to suicidality / self-harm, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 35% (18/52) During real life phase	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							4% (2/52) Statistically significant reduction (p<0.001)		
Need for mental health treatment, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 50% (26/52) During real life phase 46% (24/51) No statistically significant difference (p= 0.77)	Critical	VERY LOW
Need for treatment due to conduct problems / antisocial, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 14% (7/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.18)	Critical	VERY LOW
Need for treatment due to psychotic symptoms or psychosis, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52) During real life phase 4% (2/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
Need for treatment due to substance abuse, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 4% (2/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
Need for treatment due to autism, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 12% (6/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.30)	Critical	VERY LOW
Need for treatment due to ADHD, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 10% (5/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.09)	Critical	VERY LOW
Need for treatment due to eating disorder, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							During real life phase 2% (1/52) No statistically significant difference (p=1.0)		

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory II (BDI-II); p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; STAI: State-Trait Anxiety Inventory

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.[4] Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality).
5 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
6 Serious indirectness in Kuper et al. 2020- Outcome reported for full study cohort, of whom approximately 17% received puberty suppression alone and did not receive gender-affirming hormones
7 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 4: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Quality of life

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on quality of life (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change from baseline in mean quality of life score, measured using the QLES-Q-SF) (approximately 12-month follow-up). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=50	None	Numerical improvements in mean score reported from wave 1 (baseline) to wave 3 (approx. 12 months), but difference not statistically significant (p = 0.085) Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicated better well-being.									
1 cohort study Allen et al. 2019	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 61.70 (SE 2.43) T1 (final assessment) = 70.23 (SE 2.15) Statistically significant improvement in well-being score, p<0.002	Critical	VERY LOW

Abbreviations: GWBS: General Well-Being Scale; p: p-value; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SE: standard error

1 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Serious indirectness in Achille et al. 2020 - Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.
3 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 5: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Body image

QUALITY	Summary of findings	IMPORTANCE	CERTAINTY

					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image *(1 uncontrolled, prospective observational study)*									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=86	None	Baseline = 70.7 (SD 15.2) Follow-up = 51.4 (SD 18.3) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; p: p-value; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Table 6: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Psychological impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Psychosocial Impact (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									
Change from baseline in family functioning, measured using the Family APGAR test. Higher scores suggest more family dysfunction.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 17.9 T1 (12 months) = 18.0 No statistical analysis reported	Important	VERY LOW
Change from baseline in mean patient strengths and difficulties score, measured using the SDQ, Spanish Version (total difficulties score) (duration of treatment 12 months). Higher scores suggest the presence of a behavioural disorder.									
1 cohort study	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 14.7 (SD 3.3) T1 (12 months) = 10.3 (SD 2.9)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lopez de Lara et al. 2020							Statistically significant improvement p<0.001		
Functioning in adolescent development: Living with parent(s)/ guardians[2] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland). Not living with parent(s) or guardian in your early 20s is a marker of age-appropriate functioning in Finnish culture.									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 73% (38/52) During real life phase = 40% (21/50) Statistically significant reduction (p=0.001)	Important	VERY LOW
Functioning in adolescent development: Normative peer contacts[4] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 89% (46/52) During real life phase = 81% (42/52) Statistically significant reduction (p<0.001)	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work[5] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 64% (33/52) During real life phase = 60% (31/52) No statistically significant difference (p=0.69)	Important	VERY LOW
Functioning in adolescent development: Has been dating or had steady relationships[6] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 62% (32/50)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kaltiala et al. 2020							During real life phase = 58% (30/52) No statistically significant difference (p=0.51)		
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home[7] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[2]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 81% (42/52) During real life phase = 81% (42/52) No statistically significant difference (p=1.00)	Important	VERY LOW

Abbreviations: APGAR: Adaptability, Partnership, Growth, Affection and Resolve; p: p-value; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
2 Living arrangements were classified as (1) living with at least one parent/guardian, (2) living in a boarding school, with an adult relative, in some form of supported accommodation or the like, where supervision and guidance by a responsible adult is provided, (3) independently alone or in a shared household with a peer, (4) with a romantic partner. In the analyses dichotomised living arrangements as (a) parent(s)/guardian(s) vs. in other arrangements.
3 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
4 Peer relationships were classified as: (1) socialises with friends in leisure time, outside of activities supervised by adults, (2) socialises with peers only at school or in the context of rehabilitative activity, (3) spends time close to peers, for example in school or rehabilitative activity, but does not connect with them, (4) does not meet peers at all. In the analyses, peer relationships during (a) gender identity assessment and (b) the real-life phase were dichotomized to age-appropriate (normative) (1) vs. restricted or lacking (2–4).
5 School/work participation was classified as (1) age appropriate participation in mainstream curriculum, progresses without difficulties, (2) participates in mainstream curriculum with difficulty, (3) participates in rehabilitative educational or work activity, (4) not involved in education and working life. Age-appropriate participation during (1) was recorded if the adolescent attended mainstream secondary education or upper secondary education at a regular rate (a class per year in comprehensive school; has not changed more than once between tracks in upper secondary education) or had proceeded to work life after completing vocational education. Participation with difficulty (2) was recorded if the adolescent was enrolled in mainstream education but had to repeat a class, studied with special arrangements (for example, in a special small group), or followed some form of adjusted curriculum. In the analyses, school/work life during (a) gender identity assessment and (b) real-life phase was dichotomised to normative (1) vs. any other (2, 3 or 4).
6 Romantic involvement was recorded (1) has or has had a dating or steady relationship, not only online, (2) has had a romantic relationship only online, (3) has not had dating or steady relationships. In the analyses we compared has or has had (1) vs. has not had (2,3) a dating or steady relationship during (a) gender identity assessment and (b) real-life phase. Sexual history was recorded in more detail in case histories during gender identity assessment, and for this period we also collected the experiences of (French) kissing (yes/no), intercourse (yes/no) and experience of any genitally intimate contact with a partner (petting under clothes or naked, intercourse, oral sex) (yes/no).

7 In recording age-appropriate competence in managing everyday matters it was expected that early adolescents (up to 14 years) would be able, for example, to do shopping and travel alone on local public transport, and to help with household duties assigned by their parents. Middle adolescents (15–17 years) were further assumed, for example, to be able make telephone calls in matters important to them (for example, when seeking a summer job), to deal with school-related issues with school personnel without parental participation, to select and start new hobbies independently and to fulfil their role in summer jobs and in similar responsibilities of young people. Late adolescents (18 years and over), legally adults, were expected to have, in addition to the above, competence to talk to authorities such as professionals in health and social services, employment or educational institutions, to deal with banks or health insurance, to manage their financial issues and to manage their housekeeping if they chose to move to live independently of parents/guardians. Competence in managing everyday matters was recorded as follows: (1) the adolescent is able to cope age appropriately outside home, (2) the adolescent needs support in age-appropriate matters outside home but functions age-appropriately in the home (manages her/his own hygiene, clothing and nutrition, participates in (younger subjects) or takes responsibility for (older subjects) housekeeping) and (3) the adolescent's functioning is inadequate both at home and outside home. For the analyses, participants were determined to be able to age-appropriately able cope with matters outside of the home (1) vs. not (2,3).

Table 7: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lumbar spine bone mineral apparent density (BMAD) (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=13 (Mean) N=14 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.22 (0.02) Age 22 years: 0.23 (0.03) P=0.003 z-score (SD) Start of gender-affirming hormones: -0.90 (0.80) Age 22 years: -0.78 (1.03) No statistically significant difference	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							24-month follow-up (C24): 0.22 (0.19 to 0.27) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) 24-month follow-up (C24): -1.10 (-2.44 to 0.69) Statistically significant increase (p≤0.05)		
Change from baseline in lumbar spine BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.22 (0.19 to 0.24) 24-month follow-up (C24): 0.23 (0.21 to 0.26) Statistically significant increase (p≤0.05) z-score (range) Start of gender-affirming hormones (C0): -1.15 (-2.21 to 0.08) 24-month follow-up (C24): -0.66 (-1.66 to 0.54) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.24 (0.02) Age 22 years: 0.25 (0.28) P=0.001 z-score Start of gender-affirming hormones: -0.50 (0.81) Age 22 years: -0.033 (0.95) P=0.002	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.23 (0.19 to 0.28) 24-month follow-up (C24): 0.25 (0.22 to 0.28) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.84 (-2.2 to 0.87) 24-month follow-up (C24): -0.15 (-1.38 to 0.94) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m^3	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							Start of gender-affirming hormones (C0): 0.24 (0.20 to 0.28) 24-month follow-up (C24): 0.25 (0.21 to 0.30) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.29 (-2.28 to 0.90) 24-month follow-up (C24): -0.06 (-1.75 to 1.61) Statistically significant increase (p≤0.01)		
Change in femoral neck BMAD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=14 (Mean) N=10 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.26 (0.04) Age 22 years: 0.28 (0.05) No statistically significant difference z-score (SD) Start of gender-affirming hormones: -1.57 (1.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/m^3 C0: 0.27 (0.20 to 0.33) C24: 0.27 (0.20 to 0.36)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							No statistically significant change z-score (range) C0: -1.32 (-3.39 to 0.21) C24: -1.30 (-3.51 to 0.92) No statistically significant change		
Change from baseline in femoral neck BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/m^3 C0: 0.30 (0.26 to 0.34) C24: 0.29 (0.24 to 0.38) No statistically significant change z-score (range) C0: -0.36 (-1.50 to 0.46) C24: -0.56 (-2.17 to 1.29) No statistically significant change	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean) N=18 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.31 (0.04) Age 22 years: 0.33 (0.05) P=0.010 z-score (SD) Start of gender-affirming hormones: -0.28 (0.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/m^3 C0: 0.30 (0.22 to 0.35) C24: 0.33 (0.23 to 0.37) Statistically significant increase (p≤0.01) z-score (range) C0: -0.37 (-2.28 to 0.47) C24: -0.37 (-2.03 to 0.85) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m^3 C0: 0.30 (0.23 to 0.41) C24: 0.32 (0.23 to 0.41) Statistically significant increase (p≤0.01) z-score (range) C0: -0.27 ((-1.91 to 1.29) C24: 0.02 (-2.1 to 1.35) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change in lumbar spine BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=15 (Mean) N=13 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.84 (0.11) Age 22 years: 0.93 (0.10) P<0.001 z-score (SD)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Start of gender-affirming hormones: -1.01 (0.98) Age 22 years: -1.36 (0.83) No statistically significant difference		
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.91 (0.10) Age 22 years: 0.99 (0.13) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.72 (0.99) Age 22 years: -0.33 (1.12) No statistically significant difference	Important	VERY LOW
Change from start of testosterone treatment in lumbar spine BMD in transmen (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm^2 T0: 0.90 (0.11) T6: 0.94 (0.10) T12: 0.95 (0.09) T24: 0.95 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.81 (1.02) T6: -0.67 (0.95) T12: -0.66 (0.81) T24: -0.74 (1.17)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference from T0 to any timepoint		
Change in femoral neck BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=15 (Mean) N=11 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.87 (0.08) Age 22 years: 0.94 (0.11) P=0.009 z-score (SD) Start of gender-affirming hormones: -0.95 (0.63) Age 22 years: -0.69 (0.74) No statistically significant difference	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean) N=16 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.88 (0.09) Age 22 years: 0.95 (0.10) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.35 (0.79) Age 22 years: -0.35 (0.74) P=0.006	Important	VERY LOW
Change from start of testosterone treatment in right femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6)	None	Mean (SD), g/cm^2 T0: 0.77 (0.08)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Stoffers et al. 2019					N=37 (T12) N=15 (T24)		T6: 0.84 (0.11) T12: 0.82 (0.08) T24: 0.85 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.97 (0.79) T6: -0.54 (0.96) T12: -0.80 (0.69) T24: -0.31 (0.84) No statistically significant difference from T0 to any timepoint		
Change from start of testosterone treatment in left femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm^2 T0: 0.76 (0.09) T6: 0.83 (0.12) T12: 0.81 (0.08) T24: 0.86 (0.09) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -1.07 (0.85) T6: -0.62 (1.12) T12: -0.93 (0.63) T24: -0.20 (0.70) No statistically significant difference from T0 to any timepoint	Important	VERY LOW

Abbreviations: BMAD: bone mineral apparent density; BMD: bone mineral density; g: grams; m: metre; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)
2 Outcomes reported after gender reassignment surgery and not after gender-affirming hormones alone. Unclear whether observed changes are due to hormones or surgery
3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control)
4 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 8: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Cardiovascular risk factors

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change in body mass index (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in BMI in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +1.9 (0.6 to 3.2) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.2 (21.6 to 24.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in BMI in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +1.4 (0.8 to 2.0) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.9 (23.0 to 24.7)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Obesity rates at age 22 years (1 uncontrolled, retrospective observational study)									
Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	At 22 years, 9.9% of transfemales were obese, compared with 3.0% in reference cisgender population No statistically analysis reported	Important	VERY LOW
Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	At 22 years, 6.6% of transmales were obese, compared with 2.2% in reference cisgender population No statistically analysis reported	Important	VERY LOW
Change in blood pressure (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) -3 (-8 to 2) No statistically significant difference Mean SBP at 22 years (95% CI): 117 (113 to 122)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +6 (3 to 10) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 75 (72 to 78)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +5 (1 to 9) Statistically significant increase (p<0.05) Mean SBP at 22 years (95% CI): 126 (122 to 130)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +6 (4 to 9) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 74 (72 to 77)	Important	VERY LOW
Change in glucose levels, insulin levels, insulin resistance and HbA1c (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.1 to 0.2)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference Mean glucose level at 22 years (95% CI): 5.0 (4.8 to 5.1)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +2.7 (-1.7 to 7.1) No statistically significant difference Mean insulin level at 22 years (95% CI): 13.0 (8.4 to 17.6)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transfemales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +0.7 (-0.2 to 1.5) No statistically significant difference Mean HOMA-IR at 22 years (95% CI): 2.9 (1.9 to 3.9)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) 0.0 (-0.2 to 0.2) No statistically significant difference	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Mean glucose level at 22 years (95% CI): 4.8 (4.7 to 5.0)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -2.1 (-3.9 to -0.3) Statistically significant decrease (p<0.05) Mean insulin level at 22 years (95% CI): 8.6 (6.9 to 10.2)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transmales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): -0.5 (-1.0 to -0.1) Statistically significant decrease (p<0.05) Mean HOMA-IR at 22 years (95% CI): 1.8 (1.4 to 2.2)	Important	VERY LOW
Change from start of testosterone in HbA1c in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							statistical analysis not reported.		
Change in lipid profile (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.2 to 0.4) No statistically significant difference Mean total cholesterol at 22 years (95% CI): 4.1 (3.8 to 4.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): 0.0 (-0.1 to 0.2) No statistically significant difference Mean HDL cholesterol at 22 years (95% CI): 1.6 (1.4 to 1.7)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): 0.0 (-0.3 to 0.2) No statistically significant difference Mean LDL cholesterol at 22 years (95% CI): 2.0 (1.8 to 2.3)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.2 (0.0 to 0.5) Statistically significant increase (p<0.05) Mean triglycerides at 22 years (95% CI): 1.1 (0.9 to 1.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001) Mean total cholesterol at 22 years (95% CI): 4.6 (4.3 to 4.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -0.3 (-0.4 to -0.2) Statistically significant decrease (p<0.001) Mean HDL cholesterol at 22 years (95% CI): 1.3 (1.2 to 1.3)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Statistically significant increase (p<0.001) Mean LDL cholesterol at 22 years (95% CI): 2.6 (2.4 to 2.8)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +0.5 (0.3 to 0.7) Statistically significant increase (p<0.001) Mean triglycerides at 22 years (95% CI): 1.3 (1.1 to 1.5)	Important	VERY LOW

Abbreviations: BMI: boss mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: low-density lipoproteins; mmol/L: millimoles per litre; mU/L: milliunits per litre; SBP: systolic blood pressure; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klaver et al. (2020) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
2 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 9: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Liver enzymes (1 uncontrolled, retrospective observational study)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in alanine aminotransferase (ALT) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in gamma-glutamyl transferase (GGT) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Change from start of testosterone in alkaline phosphatase (ALP) level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12)	None	Median (IQR), U/L T0: 102 (78 to 136) T6: 115 (102 to 147) T12: 112 (88 to 143) T24: 81 (range 69 to 98)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
					N-15 (T24)		Statistically significant increase from T0 at T6 and T12 (p<0.001)		
Kidney markers (1 uncontrolled, retrospective observational study)									
Change from start of testosterone in serum creatinine level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12) N=15 (T24)	None	Mean (SD), umol/L T0: 62 (7) T6: 70 (9) T12: 74 (10) T24: 81 (10) Statistically significant increase from T0 at all timepoints (p<0.001)	Important	VERY LOW
Change from start of testosterone in serum urea[2] level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Adverse effects (1 uncontrolled, retrospective observational study)									
Permanent discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	No participants permanently discontinued gender-affirming hormones.	Important	VERY LOW
Temporary discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	3/37 transmales receiving testosterone temporarily	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Khatchadourian et al. 2014							discontinued treatment, 2 due to concomitant mental health comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment. No transfemales receiving oestrogen temporarily discontinued treatment		
Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	12/63 participants had minor complications during treatment with gender-affirming hormones All 12 were transmales receiving testosterone. Complications were severe acne (n=7), androgenic alopecia (n=1) mild dyslipidaemia (n=3) and significant mood swings (n=1) No transfemales receiving oestrogen had minor complications	Important	VERY LOW
Severe complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	No severe complications reported during gender-affirming treatment	Important	VERY LOW

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; SD: standard deviation; U/L: units per litre; umol/L: micromole per litre

1 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
2 Referred to as 'ureum' in original publication
3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)

Table 10: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Transfemales compared with transmales

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean suicidality score, measured using the ASQ tool (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	**Transfemales** T0 (baseline) = 1.21 (SE 0.36) T1 (final assessment) = 0.24 (SE 0.19) **Transmales** T0 (baseline) = 1.01 (SE 0.23) T1 (final assessment) = 0.29 (SE 0.13) No statistically significant difference in change from baseline between transfemales and transmales (p=0.79)	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicate better well-being.									
1 cohort study Allen et al. 2019	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	**Transfemales** T0 (baseline) = 58.44 (SE 4.09) T1 (final assessment) = 69.52 (SE 3.62)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
							Transmales T0 (baseline) = 64.95 (SE 2.66) T1 (final assessment) = 70.94 (SE 2.35) No statistically significant difference in change from baseline between transfemales and transmales (p=0.32)		

Abbreviations: ASQ: Ask Suicide-Screening Questions; GWBS: General Well-Being Scale; SE: standard error

1 The cohort study by Allen et al. 2019 was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 11: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth males (transfemales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=40	None	Baseline = 7.5 (SD 4.9) Follow-up = 6.6 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=45	None	Baseline = 4.2 (SD 3.2) Follow-up = 5.4 (SD 3.4)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kuper et al. 2020							No statistical analysis reported for this sub-group		
Change from baseline in mean anxiety symptoms in transfemales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 26.4 (SD 14.2) Follow-up = 24.3 (SD 15.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 5.7 (SD 4.9) Follow-up = 5.1 (SD 4.9) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 8.6 (SD 5.1) Follow-up = 8.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean social anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 7.1 (SD 3.9) Follow-up = 6.8 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean separation anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 3.4 (SD 3.3) Follow-up = 2.7 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean school avoidance symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 1.8 (SD 1.7) Follow-up = 1.9 (SD 2.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transfemales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	Wave 1 (baseline) = 11.8% (2/17) Wave 2 (approx. 12 months) = 5.9% (1/17) No statistical analysis reported	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image in transfemales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=30	None	Baseline = 67.5 (SD 19.5) Follow-up = 49.0 (SD 21.6) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 12: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth females (transmales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=76	None	Baseline = 10.4 (SD 5.0) Follow-up = 7.5 (SD 4.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=78	None	Baseline = 6.7 (SD 4.4) Follow-up = 6.2 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean anxiety symptoms in transmales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 35.4 (SD 16.5) Follow-up = 29.8 (SD 15.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 9.3 (SD 6.5) Follow-up = 7.9 (SD 6.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 10.4 (SD 5.0) Follow-up = 9.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean social anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 8.5 (SD 4.0) Follow-up = 7.8 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean separation anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 4.2 (SD 3.4) Follow-up = 3.4 (SD 2.6) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean school avoidance symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 2.9 (SD 2.3) Follow-up = 2.0 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transmales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=33	None	Wave 1 (baseline) = 9.1% (3/33) Wave 2 (approx. 12 months) = 6.1% (2/33) No statistical analysis reported	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image in transmales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 71.1 (SD 13.4) Follow-up = 52.9 (SD 16.8) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 14: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Outcomes controlled for concurrent counselling and medicines for mental health problems

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mean depression score in transfemales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.27) Numerical scores not reported	Critical	VERY LOW
Change from baseline in mean depression score in transmales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.43) Numerical scores not reported	Critical	VERY LOW
Change from baseline in depression score in transfemales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.07) Numerical scores not reported	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in depression score in transmales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.67) Numerical scores not reported	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in mean quality of life score in transfemales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.06)	Critical	VERY LOW
Change from baseline in mean quality of life score in transmales, measured using the QLES-Q-SF (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.08)	Critical	VERY LOW
Psychosocial Impact (1 uncontrolled, retrospective observational study)									
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment before or during gender identity assessment									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 47% (15/32) functioning well Did not need mental health treatment: 82% (14/17) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment before or during gender identity assessment									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=49	None	Needed mental health treatment: 72% (23/32) managing well Did not need mental health treatment: 94% (16/17) managing well No statistically significant difference p=0.06	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 42% (10/24) functioning well Did not need mental health treatment: 74% (20/27) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 67% (16/24) managing well Did not need mental health treatment: 93% (25/27) managing well Statistically significant difference p=0.02	Important	VERY LOW

Abbreviations: CESD-R: Center for Epidemiologic Studies Depression; p: p-value; PHQ 9: Patient Health Questionnaire 9; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire

1 Downgraded 1 level - the cohort study by Achille et al 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.
3 Downgraded 1 level - the cohort study by Kaltiala et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding and no control).

Table 15: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Tanner age

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mental health problems – depression, anxiety and anxiety-related symptoms (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in outcomes found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported.	Important	VERY LOW

							It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint		

Abbreviations: BIS: Body Image Scale

1 Downgraded 1 level - the cohort study by Kuper et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Glossary

Ask Suicide-Screening Questions (ASQ)	ASQ is a four-item dichotomous (yes, no) response measure with high sensitivity, designed to identify risk of suicide. A patient is considered to have screened positive if they answered yes to any item. The authors of Allen et al. 2019 altered the fourth item of the ASQ ("Have you ever tried to kill yourself?") and prefaced it with "In the past few weeks . . ." as they were not investigating lifetime suicidality. A response of 'no' was scored as 0 and a response of 'yes' was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation.
Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating bone size measurements using UK norms in growing adolescents.
Center for Epidemiologic Studies Depression scale (CESD-R)	The CESD-R is a valid, widely used tool to access depressive symptoms. The CESD-R asks about how frequently a person has felt or behaved in a certain way; with 20 questions scored from 0 score is calculated as a sum of 20 questions, ranging from 0 ("not at all or less than one day") to 3 ("5–7 days" and/or "nearly every day for 2 weeks"). Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms.
Cisgender	Cisgender is a term for someone whose gender identity matches their birth-registered sex.
Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test	The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the score: functional, 17-20 points; mildly dysfunctional, 16-13 points; moderately dysfunctional, 12-10 point; severely dysfunctional, <9 points.
Gender	The roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).

General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory score	The GWBS of the Pediatric Quality of Life Inventory uses uses a 5-point response scale, contains seven items, and measures two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. High scores reflect fewer perceived problems and greater well-being.
GnRH analogue	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of two gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in LH and FSH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Patient Health Questionnaire Modified for Teens score (PHQ 9_Modified for Teens)	The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10-14 moderate, 15-19 moderate and 20-27 severe symptoms.
Quick Inventory of Depressive Symptoms (QIDS)	Both the clinician- and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 items (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) are added to give a total score ranging from 0 to 27. A score of 0 to 5 is suggestive of no depressive symptoms, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16-20 severe symptoms and 21 to 27 very severe symptoms.
Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)	QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good).
Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire	SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders: A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these. A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this. A score of 5 or more in questions related to separation anxiety may indicate the presence of this. A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this. A score of 3 or more in questions related to significant school avoidance may indicate the presence of this.
State-Trait Anxiety Inventory (STAI) score	STAI is a validated and commonly used measure of state anxiety (current state of anxiety) and trait anxiety (general state of calmness, confidence and security). It has 40 items, the first 20 covering state anxiety, the second 20 covering trait anxiety. STAI

	can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Each subtest (state and trait) is scored between 20 and 80, with higher scores indicating greater anxiety. There is no published minimal clinically meaningful difference (MCID) for STAI or thresholds for anxiety severity.
Strengths and Difficulties Questionnaire (SDQ, Spanish version	The SDQ, Spanish version includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 is considered indicative of risk of having a disorder (normal: 0-15; borderline: 16-19, abnormal: 20-40).
Tanner stage	Tanner staging is a scale of physical development.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transfemale is a person who identifies as female and a transmale is a person who identifies as male.
Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. Higher scores indicate higher levels of gender dysphoria.

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DEFENDANT'S EXHIBIT 11

Socialstyrelsen
THE NATIONAL BOARD OF HEALTH AND WELFARE

Care of children and adolescents with gender dysphoria

Summary

Summary

The National Board of Health and Welfare (NBHW) has been commissioned by the Swedish government to update the national guidelines on care of children and adolescents with gender dysphoria, first published in 2015 [1]. Guidelines chapters are updated stepwise and this report contains revised guidance on psychosocial support and diagnostic assessment, and on puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment. This report thus replaces the corresponding chapters in the publication from 2015. Remaining chapters and the updated guidelines as a whole will be published later in 2022. In response to comments received during external review, two new chapters have been added, named *New recommendations on hormonal treatment – their reasons and consequences and Non-binary gender identity – current knowledge and a need for clarification*. Another difference compared to the guidelines from 2015 [1] is that the term "gender incongruence" is used alongside the term "gender dysphoria". For explanations of terms and abbreviations, see Appendix 2. For a description of the scientific evidence and clinical experience underlying the recommendations and the work process, see Appendices 3 and 4.

The guidelines apply to children and adolescents, i.e. people under 18 years of age. In the medical text sections, the term children (barn) refers to persons who have not yet entered puberty, while the term adolescents (ungdomar) refers to people whose puberty has started. In the text sections relating to juridical regulations, only the term children (barn) is used and denotes people younger than 18 years of age. Finally, the term "young people" (unga) is sometimes used in text sections addressing both children and adolescents.

Introductory comment

The summary that follows and the introductory chapter describe that the updated recommendations for puberty suppression with GnRH-analogues and gender-affirming hormonal treatment have become more restrictive compared to 2015, and the reasons that they have changed. The new recommendations entail that a larger

proportion than before, among adolescents with gender incongruence referred for diagnostic assessment of gender dysphoria, will need to be offered other care than hormonal treatments. Questions on how to ensure that all young people suffering from gender dysphoria be taken seriously and confirmed in their gender identity, well received and offered adequate care are becoming increasingly relevant, and will need to be answered during the ongoing restructuring of certain care for gender dysphoria into three national specialised medical care services (NBHW decision in December 2020). The care for children, adolescents and adults with gender dysphoria in these three national specialised units aims to improve equality in care, coordination and dialogue, and may enhance the implementation of national guidelines.

Recommendations and criteria for hormonal treatment

For adolescents with gender incongruence, the NBHW deems that the risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits, and that the treatments should be offered only in exceptional cases. This judgement is based mainly on three factors: the continued lack of reliable scientific evidence concerning the efficacy and the safety of both treatments [2], the new knowledge that detransition occurs among young adults [3], and the uncertainty that follows from the yet unexplained increase in the number of care seekers, an increase particularly large among adolescents registered as females at birth [4].

A systematic review published in 2022 by the Swedish Agency for Health Technology Assessment and Assessment of Social Services [2] shows that the state of knowledge largely remains unchanged compared to 2015. High quality trials such as RCTs are still lacking and the evidence on treatment efficacy and safety is still insufficient and inconclusive for all reported outcomes. Further, it is not possible to determine how common it is for adolescents who undergo gender-affirming treatment to later change their perception of their gender identity or interrupt an ongoing treatment. An important difference compared to 2015 however, is that the occurrence of

detransition among young adults is now documented [3], meaning that the uncertain evidence that indicates a low prevalence of treatment interruptions or any aspects of regret is no longer unchallenged. Although the prevalence of detransition is still unknown, the knowledge that it occurs and that genderconfirming treatment thus may lead to a deteriorating of health and quality of life (i.e. harm), is important for the overall judgement and recommendation.

To minimize the risk that a young person with gender incongruence later will regret a gender-affirming treatment, the NBHW deems that the criteria for offering GnRH-analogue and gender-affirming hormones should link more closely to those used in the Dutch protocol, where the duration of gender incongruence over time is emphasized [5-7]. Accordingly, an early (childhood) onset of gender incongruence, persistence of gender incongruence until puberty and a marked psychological strain in response to pubertal development is among the recommended criteria. The publications that describe these criteria and the treatment outcomes when given in accordance [5, 6, 8] consitute the best available knowledge and should be used as guidance.

To ensure that new knowledge is gathered, the NBHW further deems that treatment with GnRH-analogues and sex hormones for young people should be provided within a research context, which does not necessarily imply the use of randomized controlled trials (RCTs). As in other healthcare areas where it is difficult to conduct RCTs while retaining sufficient internal validity, it is also important that other prospective study designs are considered for ethical review and that register studies are made possible. Until a research study is in place, the NBHW deems that treatment with GnRH-analogues and sex hormones may be given in exceptional cases, in accordance with the updated recommendations and criteria described in the guidelines. The complex multidisciplinary assessments will eventually be carried out in the three national units that are granted permission to provide highly specialized care services.

In accordance with the DSM-5, the recommendations in the guidelines from 2015 applied to young people with gender dysphoria in general, i.e. also young people with a non-binary gender identity. Another criterion within the Dutch protocol is that the child has had a binary ("cross-gender") gender identity since childhood [5, 6].

It has emerged during the review process, that the clinical experience and documentation of puberty-suppressing and hormonal treatment for young people with non-binary gender identity is lacking, and also that it is limited for adults. The NBHW still considers that gender dysphoria rather than gender identity should determine access to care and treatment. An urgent work thus remains, to clarify criteria under which adolescents with non-binary gender identity may be offered puberty-suppressing and gender-affirming hormonal treatment within a research framework.

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DEFENDANT'S EXHIBIT 12

STM038:00/2020

Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland)

Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors

Concepts

Suppression treatment	Pubertal suppression with GnRH analogues (drugs that inhibit gonadotropin-releasing hormone activity) to halt the development of secondary sex characteristics of the biological sex.
Cisgender/Cis person	A person whose gender identity matches the sex determined at birth (identifies, and is satisfied with, the sex determined at birth and generally expresses his/her gender accordingly).
Other gender identity	A person who does not identify as a man or a woman, but rather somewhere along the continuum or outside of it; genderless, nonbinary, or multigendered.
Transgender	A person whose gender identity differs from the legal and biological sex determined at birth but instead aligns with the opposite sex.

STM038:00/2020

Content

1. Basis for Preparing These Recommendations

As the number of patients, including minors, referred to the Helsinki University Hospital (HUS) and the Tampere University Hospital (TAYS) multidisciplinary outpatient clinics for assessment and treatment of gender dysphoria has increased, PALKO (Council for Choices in Healthcare in Finland / COHERE Finland) decided to prepare recommendations for medical treatments of gender dysphoria, i.e., distress which is associated with a minor's gender variance and impairs function. Gender variance refers to a spectrum of gender experience anywhere on the male-female identity continuum or outside it, and is not exclusively confined to the dichotomized male/female conception of gender. Not all patients with gender variance experience significant suffering or functional impairments, and not all seek medical treatment.

These recommendations are based on the legislation in force at the time of the adoption of the recommendation, the available research evidence, and the clinical experience of multidisciplinary teams with expertise in gender dysphoria assessment and treatment at HUS and TAYS. The knowledge base supporting these recommendations is detailed in a separate Preparatory Memorandum and appendices and includes a description of planning and implementation of medical treatments, a literature review of medical treatments, an extensive ethical analysis, and feedback following meetings with patients and the advocacy groups who represent them.

Finnish legislation defines the requirements for the legal gender recognition of transsexuals (Act on Legal Recognition of the Gender of Transsexuals (Trans Act) 536/2002). The detailed requirements for providing the assessment and treatment to enable legal gender recognition are spelled out further in a Decree of the Ministry of Social Affairs and Health (1053/2002). The Trans Act and the related Decree apply to adults. For those who are not of legal age, there are no laws governing the provision and needs of transgender healthcare; however, these are subject to the Health Care Act of Finland (1326/2010), in particular section 7 (criteria for integrated care), section 7a (criteria for treatment options), section 8 (evidence-based, high quality, safe and appropriate care) and section 10 (rationale for centralization); and also to the Constitution of Finland (731/1999)'s section 6 on equality and section 19 on the right to adequate social and healthcare services. Finland's Act on the Status and Rights of Patients, (785/1992), and especially sections 5, 6, and 7, are also relevant.

2. Recommendations' Target Population

These recommendations apply to minors suffering from dysphoria related to gender variance who are seeking a consultation regarding an evaluation of medical examination and treatment needs; the children and adolescents may identify with the opposite sex (transgender), or may identify as genderless, non-binary, or anywhere along or outside the male/female gender identity continuum (other gender).

3. Procedures Assessed

These recommendations focus on medical treatment procedures that aim to decrease suffering and functional impairment of gender-dysphoric minors.

4. Current Care

Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty. However, in some cases, it persists or even intensifies. Gender dysphoria may also emerge or intensify at the onset of puberty. There is considerable variation in the timing of the onset of puberty in both sexes. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.

Consultation appointments (for parents / caregivers) regarding pre-pubescent children's cross-sex identification or gender dysphoria are provided by the research group on the gender identity of minors at TAYS or HUS. However, ongoing support or other treatment of psychiatric disorders are provided through the local municipal services.

In clear cases of pre-pubertal onset of gender dysphoria that intensified during puberty, a referral can be made for an assessment by the research group at TAYS or HUS regarding the appropriateness for puberty suppression. If no contraindications to early intervention are identified, pubertal suppression with GnRH analogues (to suppress the effect of gonadotropin-releasing hormone) may be considered to prevent further development of secondary sex characteristics of the biological sex.

Adolescents who have already undergone puberty, whose gender dysphoria occurs in the absence of co-occurring symptoms requiring psychiatric treatment, and whose experience of transgender identity failed to resolve following a period of reflection, can be referred for assessment by the research group on the gender identity of minors at TAYS or HUS. Hormone therapy (testosterone/estrogen and anti-androgen) can be started after the diagnostic evaluations, but no earlier than age 16. Additionally, patients under 18 receive three to six months of GnRH analogue treatment prior to the initiation of cross-sex hormones in order to suppress the hormonal activity of the gonads. No gender confirmation surgeries are performed on minors.

5. Risks, Benefits and Uncertainty

The literature review identified two studies with the total of 271 persons diagnosed with childhood-onset gender identity disorder and associated gender or body dysphoria that intensified after the onset of puberty (Preparatory Memorandum Appendix 1, Tables 15 and 16, pages 46-48).

In a smaller study of 70 adolescents, puberty was suppressed with the GnRH analogue at the average age of 14.8 (12-18 years) and puberty blockade continued for an average of 2 years. During the treatment period, the adolescents' mood improved, and the risk of behavioral disorders diminished, but gender dysphoria itself did not diminish, and there were no changes in body image. In a larger study consisting of 201 adolescents, 101 patients with the average age of 15.5 (12-18 years) started an 18-month psychological supportive intervention, and, additionally at six months, pubertal development was suppressed by starting GnRH analogue treatment. The other cohort of 100 only received psychological supportive intervention for 18 months. In both groups, statistically significant increases in global psychosocial functioning were found at 12 and 18 months; among those having received psychological intervention alone, the improvement in global functioning was already significant at the 6-month mark. Both studies lack long-term treatment follow-up into adulthood.

A recent Finnish study, published after the completion of this literature review, reported on the effect of initiating cross-sex hormone therapy on functioning, progression of developmental tasks of adolescence, and psychiatric symptoms. This study found that during cross-sex hormone therapy, problems in these areas did not decrease.

Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system. In trans girls, early pubertal suppression inhibits penile growth, requiring the use of alternative sources of tissue grafts for a potential future vaginoplasty. The effect of pubertal suppression and cross-sex hormones on fertility is not yet known.

6. Ethical Assessment

Although the ethics analysis did not systematically address the issues pertaining to children and adolescents, they have been discussed in several areas in the related documents (Preparatory Memorandum pages 52-62; Appendix 5).

According to the Health Care Act (section 8), healthcare services must be based on evidence and recognized treatment and operational practices. As far as minors are concerned, there are no medical treatment that can be considered evidence-based. At the same time, the numbers of minors developing gender dysphoria has increased. In this situation, it is vital to assure that children and young people are able to talk about their feelings, and that their feelings are acknowledged. The opportunity to reflect on one's experience should be easily accessible through the local health system (i.e., school or student health care, primary care). A young

person's feelings should not be interpreted as immediately requiring specialized medical examinations or treatments.

In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development.

From the point of view of patient advocacy groups, halting puberty is providing young people with a period of reflection, rather than consolidating their gender identity. This is based on the premise that halting the development of one's permanent sex characteristics will improve the minor's social interactions, while allowing more time for diagnostic evaluations. Additionally, patient advocacy groups assert that early intervention with hormonal treatments will lead to improved outcomes for the patients who do eventually pursue gender reassignment. Professionals, for their part, consider it important to ensure that irreversible interventions, which may also have significant adverse effects, both physical and mental, are only performed on individuals who are able to understand the permanence of the changes and the potential for harm, and who are unlikely to regret such interventions. It is not known how the hormonal suppression of puberty affects young people's judgement and decision-making.

The Act on the Status and Rights of Patients (1992/785) states that the patient shall be provided with information about his/her state of health, the significance of the treatment, various alternative forms of treatment and their effects, and about other factors concerning treatment that have an effect on treatment decision-making. In a situation where a minor's identification with the opposite sex causes long-term and severe dysphoria, it is important to make sure that he/she understands the realistic potential of gender reassignment treatments to alter secondary sex characteristics, the reality of a lifelong commitment to medical therapy, the permanence of the effects, and the possible physical and mental adverse effects of the treatments. Although patients may experience regret, after reassignment treatments, there is no going back to the non-reassigned body and its normal functions. Brain development continues until early adulthood – about age 25, which also affects young people's ability to assess the consequences of their decisions on their own future selves for rest of their lives.

A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options.

For children and adolescents, these factors are key reasons for postponing any interventions until adulthood.

7. Conclusions

The first-line intervention for gender variance during childhood and adolescent years is psychosocial support and, as necessary, gender-explorative therapy and treatment for comorbid psychiatric disorders. Uncertainty related to gender identity should be dealt with according to the severity of symptoms and the need for treatment and should be handled at the school / student health care, primary health care at the local level, or in specialty care.

In adolescents, psychiatric disorders and developmental difficulties may predispose a young person to the onset of gender dysphoria. These young people should receive treatment for their mental and behavioral health issues, and their mental health must be stable prior to the determination of their gender identity.

Clinical experience reveals that autistic spectrum disorders (ASD) are overrepresented among adolescents suffering from gender dysphoria; even if such adolescents are presenting with gender dysphoria, rehabilitative interventions for ASD must be properly addressed.

In light of available evidence, gender reassignment of minors is an experimental practice. Based on studies examining gender identity in minors, hormonal interventions may be considered before reaching adulthood in those with firmly established transgender identities, but it must be done with a great deal of caution, and no irreversible treatment should be initiated. Information about the potential harms of hormone therapies is accumulating slowly and is not systematically reported. It is critical to obtain information on the benefits and risks of these treatments in rigorous research settings.

At a minimum, a consultation for a pre- pubescent child at the specialist setting at the TAYS includes an extensive assessment appointment costing EUR 369. If necessary, a day-long outpatient consultation can be arranged, costing EUR 1,408.

The consultation and assessment process for minors at the specialist settings of TAYS or HUS costs EUR 4,300. If it is determined that this process would be untimely, the minimum cost is EUR 640. An initial assessment / consultation by phone costs EUR 100.

The planning and monitoring costs for pubertal suppression are EUR 2,000 for the first year, and EUR 1,200 for subsequent years. The costs for the planning and monitoring of hormone treatments are a minimum of EUR 400 per year.

These costs do not take into account the additional costs of psychosocial support provided in the local level, the possible need for psychiatric treatment, or hormone treatment medication costs.

8. Summary of the Recommendations

PALKO / COHERE maintains the following:

1. For the treatment of gender dysphoria due to variations in gender identity in minors, psychosocial support should be provided in school and student healthcare and in primary healthcare, and there must be sufficient competency to provide such support.
2. Consultation with a child or youth psychiatrist and the necessary psychiatric treatment and psychotherapy should be arranged locally according to the level of treatment needed.
3. If a child or young person experiencing gender-related anxiety has other simultaneous psychiatric symptoms requiring specialised medical care, treatment according to the nature and severity of the disorder must be arranged within the services of their own region, as no conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.

PALKO / COHERE considers that the consultation, periods of assessment, and treatments by the research group on the gender identity of minors at TAYS or HUS must be carried out according to the following principles:

1. Children who have not started puberty and are experiencing persistent, severe anxiety related to gender conflict and/or identification as the other sex may be sent for a consultation visit to the research group on the gender identity of minors at TAYS or HUS. Any need for support beyond the consultation visit or need for other psychiatric treatment should be addressed by local services according to the nature and severity of the problem.

2. If a child is diagnosed prior to the onset of puberty with a persistent experience of identifying as the other sex and shows symptoms of gender-related anxiety, which increases in severity in puberty, the child can be guided at the onset of puberty to the research group on the gender identity of minors at TAYS or HUS for an assessment of the need for treatment to suppress puberty. Based on these assessments, puberty suppression treatment may be initiated on a case-by-case basis after careful consideration and appropriate diagnostic examinations if the medical indications for the treatment are present and there are no contraindications. Therapeutic amenorrhea, i.e. prevention of menstruation, is also medically possible.

3. A young person who has already undergone puberty can be sent to the research clinic on the gender identity of minors at TAYS or HUS for extensive gender identity studies if the variation in gender identity and related dysphoria do not reflect the temporary search for identity typical of the development stage of adolescence and do not subside once the young person has had the opportunity to reflect on their identity but rather their identity and personality development appear to be stable.

4. Based on thorough, case-by-case consideration, the initiation of hormonal interventions that alter sex characteristics may be considered before the person is 18 years of age only if it can be ascertained that their identity as the other sex is of a permanent nature and causes severe dysphoria. In addition, it must be confirmed that the young person is able to understand the significance of irreversible treatments and the

benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present.

5. If a young person experiencing gender-related anxiety has experienced or is simultaneously experiencing psychiatric symptoms requiring specialized medical care, a gender identity assessment may be considered if the need for it continues after the other psychiatric symptoms have ceased and adolescent development is progressing normally. In this case, a young person can be sent by the specialized youth psychiatric care in their region for an extensive gender identity study by the TAYS or HUS research group on the gender identity of minors, which will begin the diagnostic studies. Based on the results of the studies, the need for and timeliness of medically justified treatments will be assessed individually.

Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors. The initiation and monitoring of hormonal treatments must be centralized at the research clinics on gender identity at HUS and TAYS.

9. Additional Evidence Gathering and Monitoring the Effectiveness of Recommendations

Moving forward, the following information must be obtained about the patients diagnosed and receiving treatments in Finland before re-evaluating these recommendations:

- Number of new patient referrals
- Number of patients starting the assessment period, and numbers of new transgender (F64.0) vs “other gender” (F64.8) diagnoses
- Whether the diagnosis remains stable or changes during the assessment phase
- Number of patients discontinuing the assessment period and the reasons for the discontinuation
- Adverse effects of treatments (especially long-term effects and effect on fertility)
- Number of patients regretting hormone therapy
- Analysis of the effects of the assessment and the treatment period on gender dysphoria outcomes, as measured by the Gender Congruence and Life Satisfaction Scale (GCLS)
- Analysis of the effects of the assessment and the treatment period on functional capacity and quality of life
- The prevalence of co-occurring psychiatric diagnoses (especially neurodevelopmental diagnoses F80-F90) among those diagnosed with / seeking treatment for gender dysphoria, and whether the presence of these co-occurring diagnoses impacts the ability to achieve the desired outcome (e.g. decreased dysphoria) in the assessment or the treatment phase.
- Whether the assessment and treatment periods lead to a reduction of suicide attempts
- Whether the assessment and treatment periods lead to a reduction in depression and distress

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10. Appendices

Preparatory Memorandum, with Appendices 1-5.

DOC. 69-13

DEFENDANT'S EXHIBIT 13

ACADÉMIE NATIONALE DE MÉDECINE

Medicine and gender transidentity in children and adolescents

Press release of the French National Academy of Medicine[1]

February 25, 2022

Gender transidentity is the strong sense, for more than 6 months, of identification with a gender different from that assigned at birth. This feeling can cause a significant and prolonged suffering, which can lead to a risk of suicide (a). No genetic predisposition has been found.

The recognition of this disharmony is not new, but a very strong increase in the demand for physicians for this reason has been observed (1, 2) in North America, then in the countries of northern Europe and, more recently, in France, particularly in children and adolescents. For example, a recent study within a dozen high schools in Pittsburgh revealed a prevalence that was much higher than previously estimated in the United States (3): 10% of students declared themselves to be transgender or non-binary or of uncertain gender (b). In 2003, the Royal Children's Hospital in Melbourne had diagnosed gender dysphoria in only one child, while today it treats nearly 200.

Whatever the mechanisms involved in the adolescent – overuse of social networks, greater social acceptability, or example in the entourage - this epidemic-like phenomenon results in the appearance of cases or even clusters in the immediate surroundings (4). This primarily social problem is based, in part, on a questioning of an excessively dichotomous vision of gender identity by some young people.

The medical demand is accompanied by an increasing supply of care, in the form of consultations or treatment in specialized clinics, because of the distress it causes rather than a mental illness per se. Many medical specialties in the field of pediatrics are concerned. First of all psychiatry, then, if the transidentity appears real or if the malaise persists, endocrinology gynecology and finally surgery are concerned.

However, a great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause. In this respect, it is important to recall the recent decision (May 2021) of the Karolinska University Hospital in Stockholm to ban the use of hormone blockers.

Although, in France, the use of hormone blockers or hormones of the opposite sex is possible with parental authorization at any age, the greatest reserve is required in their use, given the

[1] This Press release, adopted by the French Academy of Medicine on February 25, 2022, by 59 votes for, 20 against and 13 abstentions, was approved, in its revised version, by the Board of Directors on February 28, 2022.

side effects such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause.

As for surgical treatments, in particular mastectomy, which is authorized in France from the age of 14, and those involving the external genitalia (vulva, penis), their irreversible nature must be emphasized.

Therefore, faced with a request for care for this reason, it is essential to provide, first of all, a medical and psychological support to these children or adolescents, but also to their parents, especially since there is no test to distinguish a "structural" gender dysphoria from transient dysphoria in adolescence. Moreover, the risk of over-diagnosis is real, as shown by the increasing number of transgender young adults wishing to "detransition". It is therefore advisable to extend as much as possible the psychological support phase.

The National academy of medicine draws the attention of the medical community to the increasing demand for care in the context of gender transidentity in children and adolescents and recommends:

- A psychological support as long as possible for children and adolescents expressing a desire to transition and their parents;

- In the event of a persistent desire for transition, a careful decision about medical treatment with hormone blockers or hormones of the opposite sex within the framework of Multi-disciplinary Consultation Meetings;

- The introduction of an appropriate clinical training in medical studies to inform and guide young people and their families;

- The promotion of clinical and biological as well as ethical research, which is still too rare in France on this subject.

- The vigilance of parents in response to their children's questions on transidentity or their malaise, underlining the addictive character of excessive consultation of social networks which is both harmful to the psychological development of young people and responsible, for a very important part, of the growing sense of gender incongruence.

Glossary:

a. Gender dysphoria is the medical term used to describe the distress resulting from the incongruence between the felt gender and the gender assigned at birth (5).

b. A non-binary person is a person whose gender identity is neither male nor female.

c. A transgender person adopts the appearance and lifestyle of a sex different from that assigned at birth. Whether born male or female, the transgender persons changes, or even rejects, their original gender identity. The sex registered on his or her civil status does not correspond to the appearance he or she sends back. This does not necessarily lead to a therapeutic approach.

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DOC. 69-14

DEFENDANT'S EXHIBIT 14

The Royal Australian & New Zealand College of Psychiatrists

Your Health in Mind

Recognising and addressing the mental health needs of people experiencing Gender Dysphoria / Gender Incongruence

August 2021

Position statement 103

Summary

This position statement developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) provides an overview of Gender Dysphoria and highlights the importance of respecting an individual's gender identity.

Purpose

This position statement developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) provides an overview of Gender Dysphoria and highlights the importance of respecting an individual's gender identity. This statement offers insight into the key issues relevant to the mental health needs of people experiencing Gender Dysphoria and guidance is provided on how psychiatrists and mental health services can support individuals constructively. People experiencing Gender Dysphoria may experience a disproportionate level of mental illness and psychological distress. This position statement makes recommendations for enhancing the mental health sector's responsiveness to these needs.

Key messages

- Gender Dysphoria is associated with significant distress.
- There are polarised views and mixed evidence regarding treatment options for people presenting with gender identity concerns, especially children and young people. It is important to understand the different factors, complexities, theories, and research relating to Gender Dysphoria.
- It is important that there is adequate, person-centred care, for the mental health needs of people experiencing Gender Dysphoria.
- Psychiatrists play a crucial role in caring for the mental health needs of people experiencing Gender Dysphoria.
- Psychiatrists should act in a manner which is supportive, ethical, and non-judgmental.
- Comprehensive assessment is crucial. Assessment and treatment should be evidence-informed, fully explore the patient's gender identity, the context in which this has arisen, other features of mental illness

and a thorough assessment of personal and family history. This should lead to a formulation. The assessment will be always responsive to and supportive of the person's needs.
- Psychiatrists must have regard to the relevant laws and professional standards in relation to assessing capacity and obtaining consent, including the RANZCP Code of Ethics.
- Gender Dysphoria is an emerging field of research and, at present, there is a paucity of evidence. Better evidence in relation to outcomes, especially for children and adolescents is required.

Definition

Gender Dysphoria, as defined in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), refers to marked incongruence between one's experienced or expressed gender and one's assigned gender, associated with clinically significant distress or impairment in functioning.[1] Gender Incongruence is defined in the International Classification of Diseases 11th revision (ICD-11) as is 'a marked and persistent incongruence between an individual's experienced gender and the assigned sex'.[2]

Terminology

The RANZCP acknowledges the importance of using appropriate terminology when discussing issues of sexual, sex and gender identity.[3] Inclusive language engenders respect and promotes visibility for important issues, and this is integral to improving the health of LGBTIQ+ people.[4] The key terminology section below provides an overview of some key terms used in Australia and New Zealand.

It is important to be mindful of the importance of individual terminology preferences when talking about someone's sexual orientation or gender identity. Using the individual's preferred terms, especially pronouns, is very important for trans, gender diverse and non-binary people. Healthcare providers should not refer to someone using terms or pronouns that are against the individual's wishes. For example, an individual may wish to be referred to by the pronouns 'they and them' so as to avoid the gendered pronouns 'she' and 'he', and this should be respected. It is important to also be aware of the rapidity with which language and terminology can change and develop in this area, and to consider additional research or inquiry with relevant organisations as appropriate (please refer to the list of resources below for more information).

Key Terminology

- **Transphobia** encompasses a range of negative attitudes and feelings such as hatred, disgust, contempt, prejudice and fear towards people who are gender variant.
- **Trans,** or **TGD (trans and gender diverse)** are commonly used to describe a broad range of non-conforming gender identities or expressions including **transgender, agender** (having no gender), **bigender** (identifying as both a woman and a man), or **non-binary** (neither woman nor man). Some people may describe themselves as **MTF/M2F** (male-to-female), **FTM/F2M** (female-to-male), **AFAB** (assigned female at birth) or **AMAB** (assigned male at birth). The term **genderqueer** is used to refer to gender identity that does not conform to sociocultural norms. **Gender fluid** is used to refer to gender identity which shifts over time.
- For **TGDNB** (trans, gender diverse and non-binary) people, preferred pronouns may include 'he/him', 'she/her', 'they/them' or neopronouns like 'zi/zim'.
- Some Aboriginal and Torres Strait Islander peoples use the term **sistergirl** to refer to sex assigned at birth males who live partly or fully as women and **brotherboy** to refer to sex assigned at birth females who live partly or fully as men.[3]
- **Takatāpui** as a self-descriptor is often used by Māori to describe non-binary gender and/or sexual identity. Specific meaning can vary depending on context.[5] There are several Māori words for transgender people, including whakawahine (trans woman) and **whakatāne** (trans man).[6]

- In Pacific Island cultures, there are a number of gender-diverse identities including the Samoan **fa'afafine** and Tongan **fakaleiti**.[7]

Background

People experiencing Gender Dysphoria should be supported by mental health services to navigate their experience in a constructive way. Gender Dysphoria can emerge in a variety of ways. Each case should be assessed by a mental health professional, which will frequently be a psychiatrist, with the person at the centre of care. It is important the psychological state and context in which Gender Dysphoria has arisen is explored to assess the most appropriate treatment.

The views about whether psychiatric diagnosis is warranted for people who experience incongruence of gender identity are changing.[8] While 'Gender Dysphoria' is classified as a mental disorder in DSM-5, ICD-11 classifies the condition 'Gender Incongruence' not as a 'mental, behavioural and neurodevelopmental disorder' but as a 'condition related to sexual health'.[1, 2] ICD-11 has undergone significant revisions to ensure that disorders relating to sexuality and gender identity reflect contemporary evidence while appropriately distinguishing between health conditions and private behaviours.[9]

Gender Dysphoria continues to be widely debated across jurisdictions in Australia and New Zealand. The RANZCP has developed this position statement from the perspective of psychiatry.

Supporting people experiencing Gender Dysphoria/Gender Incongruence

There is evidence that people who experience incongruence between their gender identity and assigned gender have higher levels of mental illness than the general population.[10] In a retrospective study, Reisner et al (2015) found higher rates of depression, anxiety, suicidal ideation and self-harm in youth who identified as transgender.[11]

Data suggest that the number of people seeking help for gender identity issues has increased worldwide, with referrals to gender clinics increasing across age groups, including amongst children and adolescents.[12, 13] Clinics seeing young people have also reported an increasing preponderance of sex assigned at birth females among those seeking intervention and a co-occurrence of autism spectrum disorder and Gender Dysphoria. [14, 15]

Gender Dysphoria emerges in many different ways and is associated with significant distress for those who experience it. However, Gender Incongruence is not in and of itself pathological. There are polarised views and mixed evidence regarding treatment options for people presenting with gender identity concerns, especially children and young people.

The World Professional Association for Transgender Health (WPATH) uses the terminology "real life experience" defining it as "the act of fully adopting a new or evolving gender role or gender presentation in everyday life".[16] Real life experience allows transgender individuals who wish to permanently change their gender role, to transition from imagined experience to a lived experience. This experience can differ between individuals, for some the experience is liberating, whereas others can experience disappointment due to transition not living up to the desired expectation.[17]

A major challenge for clinicians working with children and adolescents who present for treatment of Gender Dysphoria is the impact of polarised socio-political discourse on clinical assessment and decision-making. Polarised views can be unhelpful and can make the task of clinicians assisting young people presenting with complex presentations more difficult.[18] Whilst these debates must be acknowledged, the most important goal currently is to ensure that there is adequate care available to meet the mental health needs of people experiencing Gender Dysphoria.

Role of psychiatrists

There are a number of guidelines and resources available which relate to Gender Dysphoria. [19-27] The RANZCP does not preference any specific guidelines. The RANZCP encourages psychiatrists to be aware there are multiple perspectives and views.

There is some evidence to suggest positive psychosocial outcomes for those who are supported in their gender identity.[28] However, evidence and professional opinion is divided as to whether an affirmative approach should be taken in relation to treatment of transgender children or whether other approaches are more appropriate.[24]

A gender affirmative approach endorses the belief system that children should be able to 'live in the gender that feels most real or comfortable to that child and to express that gender with freedom from restriction, aspersion, or rejection' therefore the child's statements regarding their gender identity should not be questioned, but instead accepted.[29] Affirmative approaches may include consideration of the need for medical treatments including gender affirming hormones, gonadotrophin releasing hormone analogues (GnRH) (in children and adolescents) and surgery. Approaches which don't include medical treatments may focus on utilising psychotherapy to aid individuals with Gender Dysphoria in exploring their gender identity, and aid alleviation of any co-existing mental health concerns identified in screening and assessment.[24]

The RANZCP endorses practice which supports and validates the identity, strength, and experience of the individual, recognising that all experiences of gender are equally healthy and valuable. In all cases, clinicians have a crucial role in empathetically supporting the individual and family/whānau assertions and lived experiences. The RANZCP acknowledges the dynamic changes in a child or adolescent's identity and brain development, appreciating the inherent complexities in the clinical care and assessment of the individual.

Mental health professionals should acknowledge the concerns of children, adolescents, and their families whilst not expressing any negative attitudes towards experiences of Gender Dysphoria. Acceptance, and alleviation of secrecy can provide relief to individuals experiencing Gender Dysphoria as well as their families.[24]

Psychiatric assessment and treatment should be both based on available evidence and allow for full exploration of the person's gender identity.[20] The RANZCP emphasises the importance of the psychiatrist's role to undertake thorough assessment and evidence-based treatment ideally as part of a multidisciplinary team, especially highlighting co-existing issues which may need addressing and treating. Psychiatric assessment and treatment must also occur in accordance with professional standards, and in a way which is person-centred, responsive to and supportive of the person's needs. Psychosocial support should be continuously offered and provided to people and their families before, during and after any treatment to maximise positive mental health outcomes.[20] If appropriate, psychiatrists can additionally facilitate the assessment of eligibility, preparation and referral for treatment.[24]

Mental health professionals including psychiatrists should maintain a collaborative and multidisciplinary approach to the treatment of Gender Dysphoria. Psychiatrists should discuss progress and obtain peer consultation from other professionals competent in the assessment and treatment of Gender Dysphoria, within both mental health and other medical disciplines.[24]

Health professionals should also be aware of ethical and medicolegal dilemmas in relation to medical and surgical treatment for people experiencing Gender Dysphoria. Psychiatrists should practise within the relevant laws and accepted professional standards in relation to assessing capacity and obtaining consent, including the RANZCP Code of Ethics.[30] Consent and authorisation for children and adolescents to commence GnRH and gender affirming hormones are subject to specific legislation in Australia and New Zealand. The legal position is rapidly changing, with the implications for policy and practice differing by jurisdiction. It is important that psychiatrists are aware of the policies and practices within the jurisdiction in which they work.

Given the complexity of these issues, it is essential that sufficient information is provided to people (and their family/whānau, or carer where relevant) to enable informed consent.[31] Further, evidence for clinical decisions about whether a child or adolescent is capable and competent to consent to treatment should be clearly recorded. In all cases, the risks and benefits of different treatments must be carefully assessed and balanced by the multidisciplinary team providing care and support to the person experiencing Gender Dysphoria.

Research on Gender Dysphoria is still emerging. At present, there is a paucity of quality evidence on the outcomes of those presenting with Gender Dysphoria. In particular, there is a need for better evidence in relation to outcomes for children and young people.[20] The RANZCP supports further research being undertaken into the long-term effects of medical and surgical affirming treatment in all age groups, including children and adolescents. Findings from the

Australian Trans20 longitudinal cohort study and Gender Identity Longitudinal Experience (GENTLE) cohort study are expected to improve our understanding.[32, 33] Such research is crucial in ensuring that individuals can safely access evidence-based therapies for Gender Dysphoria/Gender Incongruence as needed.[34, 35]

Recommendations

The RANZCP recommends the following actions to support the mental health needs of people experiencing Gender Dysphoria/Gender Incongruence:

- Psychiatrists should engage with people experiencing Gender Dysphoria in a way which is person-centred, non-judgmental and cares for their mental health needs.
- Assessment and treatment should be based on the best available evidence and fully explore the person's gender identity and the biopsychosocial context from which this has emerged.
- Health services should take steps to accommodate the needs and ensure the cultural safety of people experiencing Gender Dysphoria/Gender Incongruence.
- Further research should be supported and funded in relation to wellbeing and quality of life during and after medical and surgical interventions for Gender Dysphoria/Gender Incongruence.

Further reading

Royal Australian and New Zealand College of Psychiatrists Position Statement 83: Recognising and addressing the mental health needs of the LGBTIQ+ population

Responsible committee: Practice, Policy and Partnerships Committee

References ›

DOC. 69-15

DEFENDANT'S EXHIBIT 15

Neutral Citation Number: [2020] EWHC 3274 (Admin)

Case No: CO/60/2020

IN THE HIGH COURT OF JUSTICE
ADMINISTRATIVE COURT
DIVISIONAL COURT

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 01/12/2020

Before :

THE PRESIDENT OF THE QUEEN'S BENCH DIVISION
LORD JUSTICE LEWIS
MRS JUSTICE LIEVEN

- -

Between :

(1) QUINCY BELL
(2) MRS A

Claimants

and

THE TAVISTOCK AND PORTMAN NHS FOUNDATION TRUST

Defendant

NATIONAL HEALTH SERVICE COMMISSIONING BOARD (NHS ENGLAND)

Interested Party

(1) UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST
(2) LEEDS TEACHING HOSPITALS NHS TRUST
(3) TRANSGENDER TREND LTD

Interveners

Mr Jeremy Hyam QC and Mr Alasdair Henderson (instructed by **Sinclairslaw**) for the **Claimants**
Ms Fenella Morris QC and Ms Nicola Kohn (instructed by **DAC Beachcroft**) for the **Defendant**
The Interested Party did not appear and was not represented
Mr John McKendrick QC (instructed by **Hempsons**) for the **First and Second Interveners**
Mr Paul Skinner and Mr Aidan Wills (instructed by **Ai Law)** for the **Third Intervener**
Hearing dates: **7 and 8 October 2020**

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE PRESIDENT OF THE QUEEN'S BENCH DIVISION
LORD JUSTICE LEWIS
MRS JUSTICE LIEVEN

Dame Victoria Sharp P., Lord Justice Lewis, Lieven J.

SECTION A: INTRODUCTION AND BACKGROUND

1. This is the judgment of the court.

2. This is a claim for judicial review of the practice of the defendant, the Tavistock and Portman NHS Foundation Trust, through its Gender Identity Development Service (GIDS) and the first and second Interveners (the Trusts) of prescribing puberty-suppressing drugs to persons under the age of 18 who experience gender dysphoria.

3. Gender dysphoria or GD is a condition where persons experience distress because of a mismatch between their perceived identity and their natal sex, that is, their sex at birth. Such persons have a strong desire to live according to their perceived identity rather than their natal sex.

4. Those with gender dysphoria may be referred to GIDS. GIDS may, in turn, refer them to one of two NHS Trusts (the first and second Interveners) whose clinicians may be prepared to undertake medical interventions in relation to those with gender dysphoria. We are concerned in this case with the administration of gonadotropin-releasing hormone agonists (GnRHa) which are hormone or puberty blocking drugs (also called PBs) to suppress the physical developments that would otherwise occur during puberty.

5. Puberty blocking drugs can in theory be, and have in practice been, prescribed for gender dysphoria through the services provided by the defendant to children as young as 10. It is the practice of the defendant, through GIDS, to require the informed consent of those children and young persons to whom such drugs are prescribed.

6. The issue at the heart of this claim is whether informed consent in the legal sense can be given by such children and young persons.

7. The claimants' case is that children and young persons under 18 are not competent to give consent to the administration of puberty blocking drugs. Further, they contend that the information given to those under 18 by the defendant is misleading and insufficient to ensure such children or young persons are able to give informed consent. They further contend that the absence of procedural safeguards, and the inadequacy of the information provided, results in an infringement of the rights of such children and young persons under Article 8 of the European Convention for the Protection of Human Rights and Fundamental Freedoms (the Convention).

8. In our view, it is appropriate to consider first, whether a child under 16, or a young person between 16 and 18, can give the requisite consent; and secondly, if, in principle, they can do so, whether the information provided by the defendant and the Trusts is adequate for achieving informed consent.

9. The court in this case is concerned with the legal requirements of the process of obtaining consent for the carrying out of medical treatment. In considering this issue the court has had to consider evidence on the use of PBs, their impact on the patients, both in the short and long term, and the evidence of the efficacy of their use. The court is not deciding on the benefits or disbenefits of treating children with GD with PBs, whether in the long or short term. The court has been given a great deal of evidence

about the nature of GD and the treatments that may or may not be appropriate. That is not a matter for us. The sole legal issue in the case is the circumstances in which a child or young person may be competent to give valid consent to treatment in law and the process by which consent to the treatment is obtained.

10. We have had placed before us written evidence from a wide variety of those engaged in issues surrounding GD and a number of individuals who have been treated or are still being treated with PBs.

11. On behalf of the defendant and the Trusts there are statements from Dr Polly Carmichael, Director of GIDS, Professor Gary Butler, Consultant in Paediatric Endocrinology at University College Hospital London, and Dr Nurus-Sabah Alvi, Consultant in Paediatric Endocrinology at Leeds General Infirmary and Clinical Lead for Endocrine Liaison Clinics of the GIDS, Leeds. These witnesses describe the process that the children and young people go through at GIDS and at the Trusts. The court has also had a wide range of evidence from a variety of people concerned with the treatment of those under 18 with PBs. We will refer to that evidence and its sources as appropriate below. Our references to a child or children will be to those under the age of 16, and to young person(s) to anyone under the age of 18, save where it is clear from the context that we are referring to anyone under the age of 18.

Gender Dysphoria

12. Gender dysphoria is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which provides for one overarching diagnosis of gender dysphoria with separate specific criteria for children and for adolescents and adults:

> "In adolescents and adults gender dysphoria diagnosis involves a difference between one's experienced gender and assigned gender, and significant distress or problems functioning. It lasts at least six months and is shown by at least two of the following:
>
> 1. A marked incongruence between one's experienced / expressed gender and primary and / or secondary sex characteristics
>
> 2. A strong desire to be rid of one's primary and / or secondary sex characteristics
>
> 3. A strong desire for the primary and / or secondary sex characteristics of the other gender
>
> 4. A strong desire to be of the other gender
>
> 5. A strong desire to be treated as the other gender
>
> 6. A strong conviction that one has the typical feelings and reactions of the other gender.
>
> In children, gender dysphoria diagnosis involves at least six of the following and an associated significant distress or impairment in function, lasting at least six months:

1. A strong desire to be of the other gender or an insistence that one is the other gender

2. A strong preference for wearing clothes typical of the other gender

3. A strong preference for cross-gender roles in make-believe play or fantasy play

4. A strong preference for toys, games or activities stereotypically used or engaged in by the other gender

5. A strong preference for playmates of the other gender

6. A strong rejection of toys, games and activities typical of one's assigned gender

7. A strong dislike of one's sexual anatomy

8. A strong desire for the physical sex characteristics that match one's experienced gender."

Gender Identity Development Service (GIDS)

13. The defendant is an NHS Foundation Trust employing specialist staff including child psychologists, psychotherapists, psychiatrists, social workers, family therapists and nurses. Since 1989 it has provided a gender identity development service, a specialised service providing care to patients up to the age of 18 suffering from GD. GIDS is commissioned by the National Health Service Commissioning Board. The statutory mechanism is that under section 3B of the NHS Act 2006, the Secretary of State has the power to require NHS England to arrange services or facilities as may be prescribed by regulations. The Secretary of State has exercised that power (pursuant to Regulation 11 of the National Health Service Commissioning Board and Clinical Commissioning Groups (Responsibilities and Standing Rules) Regulations 2012/2296, which concerns specified services for rare and very rare conditions) that NHS England must arrange for the provision of services including, pursuant to para 56 of Schedule 4, a gender identity development service specifically for children and adolescents in addition to gender dysphoria services more generally (para 57).

14. Schedule 2, Part A of the NHS Standard Contract, pursuant to which GIDS is provided, sets out the Service Specification which establishes the context of the service, its aims and objectives and the manner in which it will be delivered. As set out in the Service Specification, the service is commissioned to provide specialist assessment, consultation and care including psychological support and physical treatments. The purpose of the treatment is *"to help reduce the distressing feelings of a mismatch between their natal (assigned) sex and their gender identity."* The service also provides support to family and carers of children and young persons so affected.

15. GIDS recognises three stages of physical intervention that may be appropriate in cases of GD. Stage 1 is the administration of GnRHa (one form of puberty blocker). This is clinically appropriate for children and young people who have reached Tanner Stage 2

of puberty and above. Tanner Stage 2 marks the beginning of the physical development of puberty. In natal girls this is the start of development of the breasts, and in boys the testicles and scrotum begin to get larger. Stage 2 of the treatment is the administration of cross-sex hormones (CSH) which can only be prescribed from around the age of 16. Stage 3 is gender reassignment surgery which is only available via adult services to people aged over 18.

16. GIDS takes referrals from across England and Wales and from a wide range of professionals in the health, social services and education sectors, and the voluntary sectors. When a referral is made, the case will be discussed with the relevant regional team. If the intake is successful, then the child will then progress to the GIDS waiting list.

17. As at November 2019 the waiting time for a first assessment at GIDS was between 22-26 months. When a young person reaches the top of the waiting list, they will be invited to the first of a number of assessment appointments at GIDS. The assessment process laid out in the Service Specification anticipates that the assessment process will typically span three to six sessions over 6 months or longer. Most young people will have more sessions than this, and the younger the age the more sessions are likely.

18. Dr Carmichael said that during assessments young persons will be asked, for example, about: the onset of their gender dysphoria; the consistency of their feelings about their gender; how they identify (cross-gender, non-binary, etc); their relationships with peers and family members; their social functioning in general, thoughts about or experience of puberty; their relationship to their bodies; their attractions or romantic relationships as appropriate based on their age and maturity; and their hopes and expectations for the future.

19. As this case is brought by way of judicial review of the GIDS policy and practice, rather than a challenge to an individual treatment decision, it is not possible to give a detailed analysis of the facts of an individual case and the degree to which all the matters referred to by Dr Carmichael were explored in the particular case. We refer at paras 78 to 89 below to the evidence of the experience of the first claimant and some of the other patients of the GIDS service.

20. Dr Carmichael sets out the broad range of professionals who work within GIDS, their specialism in working with young people with GD and the care that is taken when discussing the young person's expression of their gender identity.

21. At the end of the assessment period the clinicians will agree a care plan with the young person and their family. Where the young person fulfils the criteria in the Service Specification and has reached at least Tanner Stage 2 of puberty, they will be referred by GIDS to the first and second Interveners for consultation and/or physical assessment with endocrinologists with a view to being prescribed PBs. Dr Carmichael explains that before any referral to the Trusts, GIDS clinicians discuss the treatment with the young person, including explaining side effects.

The Age and Patient Group for Puberty Blockers

22. Until 2011 PBs were only available at GIDS for those aged 16 or older. In 2011 PBs started to be prescribed for those aged 12-15 and in mid-puberty. This was first done between 2011-14 at University College London Hospital (UCLH) under an approved research study known as the Early Intervention Study. The Study took an uncontrolled treatment cohort of 12-15 year olds with established and persistent GD in England. The Study recruited children for 3 years, but there was then a period until February 2019 when the last cohort member began the next stage of therapy (cross-sex hormones).

23. One of the issues raised in these proceedings is the non-existent or poor evidence base, as it is said to be, for the efficacy of such treatment for children and young persons with GD.

24. In that context, we note that though this research study was commenced some 9 years ago, at the time of the hearing before us the results of this research had yet to be published. Dr Carmichael says in her witness statement dated 2 February 2020 that a paper is now being finalised for publication. At the hearing we were told that that this paper had been submitted for peer-review but that Professor Viner, one of the authors of it, had yet to respond to issues raised by the reviewers, as he has been otherwise engaged in working on issues relating to the coronavirus pandemic.

25. The court was however provided with a paper entitled *"The Early Intervention Study. An evaluation of early pubertal suppression in a carefully selected group of adolescents with "Gender Identity Disorder". A statement and update on the Early Intervention Study (dated 2020)".* We refer further to this paper at para 73 below.

26. There are now two types of endocrine clinic: a clinic for under 15s, referred to as the early intervention clinic, and a clinic for over 15s. The Service Specification states that the early intervention clinic will continue to follow the 2011 Protocol, save that PBs will now be considered for any children *under the age of 12* if they are in established puberty.

27. The age distribution of those treated with PBs in each year between 2011 and 2020 was not provided to the court. Although the defendant and the Trusts said that such data was available, in the sense that the ages of the children are known, the data has not been collated for each year. However, Ms Ailsa Swarbrick, the Divisional Director of Gender Services at the Trust, has presented evidence in relation to patients referred to endocrinology services in 2019-20 and those treated in earlier years but who were discharged from GIDS in 2019-2020. This work was done in response to recommendations in the GIDS Review Action Plan 2019 (a Review commissioned by the Trust following a report by Dr David Bell) that data would help to inform clinical and service developments and a process of continuous improvement.

28. We note here that we find it surprising that such data was not collated in previous years given the young age of the patient group, the experimental nature of the treatment and the profound impact that it has.

29. As it is, for the year 2019/2020, 161 children were referred by GIDS for puberty blockers (a further 10 were referred for other reasons). Of those 161, the age profile is as follows:

> 3 were 10 or 11 years old at the time of referral;
>
> 13 were 12 years old;
>
> 10 were 13 years old;
>
> 24 were 14 years old;
>
> 45 were 15 years old;
>
> 51 were 16 years old;
>
> 15 were 17 or 18 years old.

For the year 2019/20, therefore, 26 of the 161 children referred were 13 or younger; and 95 of the 161 (well over 50%) were under the age of 16.

30. It follows from the information that the court does have on age distribution that some young people could be on PBs for a number of years, in the most extreme case for 5 years between the age of 10 and when they start CSH at 16.

31. Apart from the age distribution, there are other aspects of the patient group which are relevant to this case. The number of referrals to GIDS has increased very significantly in recent years. In 2009, 97 children and young people were referred. In 2018 that number was 2519.

32. Further, in 2011 the gender split was roughly 50/50 between natal girls and boys. However, in 2019 the split had changed so that 76 per cent of referrals were natal females. That change in the proportion of natal girls to boys is reflected in the statistics from the Netherlands (Brik et al "*Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria"* 2018). The defendant did not put forward any clinical explanation as to why there had been this significant change in the patient group over a relatively short time.

33. It is recorded in the GIDS Service Specification and the wider literature that a significant proportion of those presenting with GD have a diagnosis of Autistic Spectrum Disorder (ASD). The Service Specification says:

> "There seems to be a higher prevalence of autistic spectrum disorder (ASD) conditions in clinically referred, gender dysphoric adolescents than in the general adolescent population. Holt, Skagerberg & Dunsford (2014) found that 13.3% of referrals to the service in 2012 mentioned comorbid ASD (although this is likely to be an underestimate). This compares with 9.4% in the Dutch service; whereas in the Finnish service, 26% of adolescents were diagnosed to be on the autism spectrum (Kaltiala-Heino et al. 2015)."

34. The court asked for statistics on the number or proportion of young people referred by GIDS for PBs who had a diagnosis of ASD. Ms Morris said that such data was not available, although it would have been recorded on individual patient records. We therefore do not know the proportion of those who were found by GIDS to be *Gillick* competent who had ASD, or indeed a mental health diagnosis.

35. Again, we have found this lack of data analysis – and the apparent lack of investigation of this issue - surprising.

The process of taking consent

36. The position taken by GIDS is that they will only refer a young person for PBs if they determine that person is competent to give consent, i.e. is *Gillick* competent within the meaning of competence identified in the decision of the House of Lords in *Gillick v West Norfolk and Wisbech Health Authority* [1986] AC 112.

37. Dr Carmichael explained that GIDS takes consent from the young person to their case being referred to the Trusts for treatment; however the consent for the actual prescription of the PBs is taken separately by the clinicians working for the Trusts. She set out the careful process by which GIDS gives information to the young persons and to their parents in order to seek to ensure that the young person is in a position to give valid consent. The court was taken through the statements of Dr Carmichael and Professor Butler and various documents to show the level of information and dialogue that was involved in achieving lawful consent to the treatment. The Service Specification includes Section 3.2 on "Informed Consent". This states *"The consequences of treatment decisions can be significant and life-changing"* and states:

> "All efforts will be made to ensure that clients are aware of the longer term consequences of the endocrine treatments, including implications for fertility, and the decision of the competence of the client will be jointly made by the endocrine and psychological members of the Service's integrated team.
>
> The current context of treatment decisions about cross sex hormones in adolescence is that there is limited scientific evidence for the long-term benefits versus the potential harms of the intervention. There are also concerns that it is uncertain whether or not a young person will continue to identify as transgender in the future, given that some subsequently identify in a different way."

38. The defendant has recently adopted a Standard Operating Procedure for the taking of consent in GIDS. This has taken 2 years to develop and is dated 31 January 2020. Dr Carmichael says at para 33 of her first statement:

> "In advance of any referral by the Trust of a young person for consideration by an endocrinologist for GnRHa treatment, GIDS clinicians discuss treatment with the young person. This includes, checking that the young person's hopes for treatment are realistic, explaining what the treatment can and cannot do, discussing any potential

> side-effects, discussing fertility and potential impact on genital development for birth registered males. We have developed visual aids to support this process.
>
> UCLH and LTH have collated extensive written information to help young people and their parents further understand the nature of the drugs, their limitations and the possible side effects. These written documents are given to young people at their first endocrine clinic visit. The written documents act as a reference point for patients with questions whilst they contemplate whether they would like to go ahead with the referral, and subsequently with treatment. In particular, informational slides titled "Have you thought about having children in the future?" explains the impact GnRHa treatment can have on fertility in explicit terms. Young people and their families are encouraged to raise any questions with their GIDS clinicians or at their next endocrine clinic visit."

39. Ms Morris emphasised that the process of ensuring that consent could validly be given was a discursive and iterative one that involved multiple discussions and answering any questions the young people or their parents might raise. Dr Carmichael said at para 35: "*The GIDS clinicians make it very clear to children and young people that there are both known and unknown risks associated with GnRHa treatment."* Further, she said at para 41: "*In my experience, those young people we see who are recommended for GnRHa treatment understand the implications and limitations of treatment with GnRHa treatment and are able to consent to this stage of treatment."*

40. Professor Butler described the approach to consent at the Trusts as follows:

> "For those under 15 years of age all the pre-assessment consultations are individual and occur with a consultant or senior clinical fellow on at least two visits. Parental support (or that of their guardian or social services where appropriate) is a pre-requisite for the under 15 year stream. On occasions, a young person is not deemed, on clinical examination, to be at an appropriate stage of puberty so further follow-up visits are arranged thereafter at 6-12 monthly intervals until a person is deemed at an appropriate physical stage for intervention and taking of consent. This also gives the opportunity to judge the level of emotional cognitive and psychosocial maturity, and capacity.
>
> The decisions at UCLH and Leeds do not automatically follow on from those made at the GIDS Tavistock. They are a reassessment of physical maturity and cognitive capacity in their own right. They may be at odds with the Tavistock formulation (an infrequent event) and thus would be returned to the Tavistock MDT for reconsideration."

41. Professor Butler said that in his clinic they are careful to ensure that the force behind the decision to seek treatment comes from the young person themselves and is not a consequence of pressure upon them from others around them. The Trusts work closely

with parents to reach a solution that is satisfactory to all and meets the best interests of the child. His clinic has never sought to apply to the Court under its inherent jurisdiction "against" parental opinions because he is concerned that would cause familial frictions. Equally, he suggested UCLH would not wish to have to apply to the court for consent on behalf of the child because it would delay treatment and put an additional burden on GIDS and the Trusts; and because "*it would also increase the distress suffered by the young people themselves, finding that their right to autonomous decision making had been removed from them.*"

42. Professor Butler said a full written information package is provided to older adolescents. For those under 15 there is an initial individual consultation because of the need for "*individualising the approach for very young people, taking special care to assess their level of knowledge and understanding and they are given the written information package then.*" In relation to impacts on fertility and sexual functioning he says:

> "It is also relevant for the consultation purposes that matters of fertility are discussed and counselling by the team takes place, and the option of meeting a fertility specialist is offered, and often taken up. The options of fertility preservation are discussed with all the young people and it is a requirement of the consent process that they fully understand this at an age appropriate level. This understanding must include that they are unable to have the typical sexual relationship of their identified gender with another person on account of their biological sex organ development, and that other surgical procedures may be necessary later on to achieve this possibility."

43. He then said: "*it is an absolute requirement before starting any treatment that a young person can fully understand this effect on fertility and sexual functioning according to their age and level of maturation.*"

44. The court asked for statistical material on the number, if any, of young people who had been assessed to be suitable for PBs but who were *not* prescribed them because the young person was considered not to be *Gillick* competent to make the decision, whether at GIDS or the Trusts. Ms Morris could not produce any statistics on whether this situation had ever arisen. She suggested that in the main, GIDS would work with the young person to give them further information, discuss the matter further and in some cases wait until they had achieved further maturity. The court gained the strong impression from the evidence and from those submissions that it was extremely unusual for either GIDS or the Trusts to refuse to give PBs on the ground that the young person was not competent to give consent. The approach adopted appears to be to continue giving the child more information and to have more discussions until s/he is considered *Gillick* competent or is discharged.

45. Relevant to the evidence of consent is the evidence of Professor Scott (Director of University College London's Institute of Cognitive Neuroscience). She *"seeks to explain, from a neuroscientific point of view, why I have significant doubts about the ability of young people under the age of 18 years old to adequately weigh and*

appreciate the significant consequences that will result from the decision to accept hormonal treatment for gender dysphoria."

46. She explained the neurological development of adolescents' brains that leads to teenagers making different, more risky decisions than adults. She said further that this is backed up by behavioural studies showing that when decision making is "hot" (i.e. more emotional), under 18 year olds make less rational decisions than when the responses are made in a colder, less emotional context. Her conclusion was that:

> "11. … given the risk of puberty blocking treatment, and the fact that these will have irreversible effects, that have life-long consequences, it is my view that even if the risks are well explained, that in the light of the scientific literature, that it is very possible for an adolescent to be unable to fully grasp the implications of puberty-blocking treatment. All the evidence we have suggests that the complex, emotionally charged decisions required to engage with this treatment are not yet acquired as a skill at this age, both in terms of brain maturation and in terms of behaviour."

Parental consent

47. If a child cannot give consent for treatment because they are not *Gillick* competent then the normal position in law would be that someone with parental responsibility could consent on their behalf. Mr Hyam sought at one point to argue that a decision as to giving PBs would fall outside the scope of parental responsibility because of the nature of the treatment concerned. However, the GIDS practice in relation to acting on parental consent alone is quite clear. In the response to the pre-action protocol letter the defendant said:

> "36. There is a fundamental misunderstanding in your letter, which states that parents can consent to pubertal suspension on behalf of a child who is not capable of doing so. This is not the case for this service, as is clear from the above. Although the general law would permit parent(s) to consent on behalf of their child, GIDS has never administered, nor can it conceive of any situation where it would be appropriate to administer blockers on a patient without their consent. The Service Specification confirms that this is the case."

It follows that is not necessary for us to consider whether parents could consent to the treatment if the child cannot lawfully do so because this is not the policy or practice of the defendant and such a case could not currently arise on the facts.

The effect of Puberty Blockers

48. PBs have been used for many years to stop precocious puberty. This is a condition experienced largely by children aged 7 or under when puberty commences at a very early age. This condition is seen more often in natal girls but sometimes in natal boys. PBs are used to stop this early onset of puberty and the use of them ceases when the child reaches an appropriate age for puberty. As can be seen from the evidence this use of PBs does not interfere with the onset of puberty at a normal biological age and, as such, will not interfere with normal development of puberty through adolescence.

49. The use of PBs in cases of GD is quite different. We have some evidence of the history of this treatment and the meaning of puberty from Professor Hruz (Associate Professor of Paediatrics, Endocrinology and Diabetes at Washington University, St Louis, USA) on behalf of the claimants.

50. In summary, PBs were first used for such treatment at a Dutch gender clinic in the late 1990s. That clinic developed a protocol, often referred to as the Dutch protocol. The Dutch protocol was published in the European Journal of Endocrinology in 2006 and called for puberty suppression to begin at the age of 12 after a diagnosis of GD. Puberty is understood in medicine or biology as a process of physiological change involving the process of maturation of the gonads. Hormones in a part of the brain secrete a gonadotropin-releasing hormone which, in turn, stimulates the pituitary gland to secrete other hormones. These stimulate the growth of the gonads, that is ovaries in females and testes in males. Further hormones are secreted which contribute to the further development of the primary sex characteristics, the uterus in females and the penis and scrotum in males. The hormones contribute to the development of secondary sex characteristics including breasts and wider hips in girls and wider shoulders, deeper voices and increased muscle mass in boys. Further growth hormones are released, which stimulate growth. With regular injection of the PBs there is no progression of puberty and some regression of the first stages of already developed sexual characteristics. This means that in girls *"breast tissue will become weak and may disappear completely"* and in boys *"testicular volume will regress to a lower volume."*

51. Under the Dutch protocol, the introduction of CSH starts at age 16. As Professor Hruz explained:

> "29. Then, starting at age 16, cross-sex hormones are administered while GnRH analogue treatment continues, in order to induce something like the process of puberty that would normally occur for members of the opposite sex. In female-to-male patients, testosterone administration leads to the development of "a low voice, facial and body hair growth, and a more masculine body shape" as well as to clitoral engagement and further atrophying of breast tissue. In patients seeking a male-to-female transition, the administration of estrogens will result in "breast development and a female-appearing body shape." Cross-sex hormone administration for these patients will be prescribed for the rest of their lives."

52. There is some dispute as to the purpose of prescribing PBs. According to Dr Carmichael, the primary purpose of PBs is to give the young person time to think about their gender identity. This is a phrase which is repeated on a number of the GIDS and Trust information documents. The Health Research Authority carried out an investigation into the Early Intervention Study in 2019. Its report was somewhat critical of the description of the purpose and said:

> "The research team described the purpose of pubertal suppression as 'to induce a sex hormone-neutral environment to provide young people with space to decide whether to progress further with gender reassignment treatment as an adult.' This phrase appears to have caused confusion as it has been interpreted by some that the puberty suppression was for use in

> any children presenting to the clinic, that there would be no change in the course of any gender identity dysphoria during this time, and that the child could then choose to progress to cross-sex hormone treatment or to stop treatment with subsequent onset of puberty in the birth gender. It has been noted that the participants in this study and other research involving early puberty suppression have progressed to cross-sex hormones. This has raised concerns that the treatment might be responsible for generating persistence, rather than 'creating space to decide'.
>
> It would have reduced confusion if the purpose of the treatment had been described as being offered specifically to children demonstrating a strong and persistent gender identity dysphoria at an early stage in puberty, such that the suppression of puberty would allow subsequent cross-sex hormone treatment without the need to surgically reverse or otherwise mask the unwanted physical effects of puberty in the birth gender. The present study was not designed to investigate the implications on persistence or desistence of offering puberty suppression to a wider range of patients, it was limited to a group that had already demonstrated persistence and were actively requesting puberty blockers."

53. Professor Butler said that PBs:

> "may have some help or advantage in the support of transgender adolescents in some aspects of mental health functioning, in particular with reducing the risk of reduction of suicidal ideation and actual suicidal actions themselves."

54. See further the reference at para 73 below to the paper presented by Dr Carmichael and Professor Viner in 2014, referring to the Early Intervention Study and the limited evidence of psychological benefit.

55. As is clear from the literature and referred to by the HRA, the other purpose of giving PBs is stopping the development of the physical effects of puberty (something that obviously varies depending on at what age and stage in pubertal development the PBs are commenced) because slowing or preventing the early development of secondary sex characteristics during puberty can make a later transition (both medical and social) to living as the opposite sex easier.

The relationship between Puberty Blockers and Cross-Sex Hormones (CSH)

56. GIDS and the Trust place reliance on the fact that Stage 1 treatment with PBs and Stage 2 treatment (CSH) are separate. Thus, so it is said, it is possible for a young person to come off the PBs at any point and not proceed to taking CSH. On one view, this is correct. However, the evidence that we have on this issue clearly shows that practically all children / young people who start PBs progress on to CSH.

57. No precise numbers are available from GIDS (as to the percentage of patients who proceed from PBs to CSH). There was some evidence based on a random sample of those who in 2019-2020 had been discharged or had what is described as a closing summary from GIDS. However the court did have the evidence of Dr de Vries. Dr de Vries is a founding board member of EPATH (European Professional Association for Transgender Health) and a member of the WPATH (World Professional Association for Transgender Health) Committee on Children and Adolescents and its Chair between 2010 and 2016, and leads the Centre of Expertise on Gender Dysphoria at the Amsterdam University Medical Centre in the Netherlands (CEGD). This is the institution which has led the way in the use of PBs for young people in the Netherlands; and is the sole source of published peer reviewed data (in respect of the treatment we are considering) produced to the court. She says that of the adolescents who started puberty suppression, only 1.9 per cent stopped the treatment and did not proceed to CSH.

58. We were told that the defendant did not have any data recording the proportion of those on puberty blockers who progress to cross-sex hormones. We were told that in part this resulted from the fact that some would have progressed to adult services and would not be recorded by the defendant. Ms Swarbrick had carried out an analysis of a random sample of 312 of 1648 files of patients discharged from GIDS from 1st March 2019 to 4th March 2020. Dr Carmichael summarised this as:

> "…based on a random sample of those referred to GIDS who had been discharged or had a closing summary from GIDS in 19-20 (analysis B) 16% of patients (49 individuals) had accessed the endocrinology service during their time with GIDS. Of those 16%, 55% (27 individuals) were subsequently approved for or accessed cross-sex hormones during their time with GIDS. This number represents 8.7% of all the patients discharged from GIDS that year. We also know that of the 49 patients who were referred to endocrinology for GnRHa whilst at GIDS, two did not commence GnRHa treatment, and a further five were discharged from GIDS without being referred on to another gender service."

59. We find it surprising that GIDS did not obtain full data showing the figures and the proportion of those on puberty blockers who remain within GIDS and move on to cross-sex hormones. Although neither Dr Carmichael nor Professor Butler could give the equivalent figures in the United Kingdom to those from the Netherlands, the language used in their witness statements suggests that a similarly high proportion of children and young people in the United Kingdom move from PBs onto CSH.

The impact of Puberty Blockers and their reversibility

60. Both WPATH and the Endocrine Society in their documentation describe PBs as fully reversible. Professor Butler says that "*we do not know everything about the blocker and as far as we know it is a safe reversible treatment with a well-established history."* Dr Alvi also referred to the history of the use of PBs as showing that they are fully reversible. However, it is important to note that apart from the Amsterdam study, the history of the use of PBs relied upon in this context is *from the treatment of precocious*

puberty which is a different condition from GD, and where PBs are used in a very different way.

61. Dr de Vries was somewhat more nuanced in her evidence. She said:

> "Puberty blocking treatment is fully reversible (see for example section 2.0 of the Endocrine Society's Clinical Practice Guidelines…). By fully reversible I mean that the administration of puberty blockers in young people has no irreversible physical consequences, for example for fertility, voice deepening or breast growth".

62. At para 20 of her evidence she said:

> "Ethical dilemmas continue to exist around … the uncertainty of apparent long-term physical consequences of puberty blocking on bone density, fertility, brain development and surgical options."

63. The GIDS Early Intervention Young Person Information Sheet states:

> "What are the possible benefits of starting on hormone blockers?
>
> We have looked at other countries who have given this treatment **and the results** suggest that:
>
> - Hormone blockers which block the body's natural sex hormones may improve the way you feel about yourself.
> - If you decide to stop the hormone blockers early **your physical development** will return as usual in your natal gender. **As far as we are aware**, the hormone blockers will not harm your physical or psychological development.
> - Hormone blockers will make you feel less worried about growing up in the wrong body and will give you more time and space to think about your gender identity.
>
> What are the possible disadvantages and risks of the hormone blockers?
>
> - Possible side effects from the hormone blockers are hot flushes, headache, nausea and weight gain.
> - A short term effect is that your bone strength is shown not to grow as fast as it usually would whilst you are on hormone blockers. However, this will resume once your body is exposed to hormones again. That is why we have to do a bone scan every year to check the thickness of your bones. **We do not fully know how hormone blockers will affect bone strength, the development of your sexual organs, body shape or your final adult height. There**

> **could be other long-term effects of hormone blockers in early puberty that we don't yet know about.**
>
> - Hormone blockers could affect your memory, your concentration or the way you feel about your gender and how likely you are to change your mind about your gender identity.
>
> - Hormone blockers could affect your ability to have a baby. It could take 6 to 12 months longer after stopping the hormone blockers before natal boys start making sperm again or natal girls start maturing eggs in their ovaries. However, hormone blockers do not work as a contraceptive. If you are sexually active, please ask your doctor for advice about birth control." (emphasis added)

64. A number of aspects of this asserted reversibility are raised by the claimants. PBs stop the physical changes in the body when going through puberty. But in reliance on the evidence of Professor Levine (Clinical Professor of Psychiatry at Western Reserve University, Ohio) and Professor Hruz, the claimants assert that neurological and psychological changes occurring in puberty are less well understood than the physiological changes. Further, the degree to which neurological differences are caused by biological factors like hormones and genes are matters of debate. Professor Levine set out evidence on the degree to which young people mature through adolescence through both social and personal experiences. For young people on PBs that maturing process is stopped or delayed with potential social and psychological impacts which could be described as non-reversible.

65. Thus, the central point made by the claimants is that although most of the physical consequences of taking PBs may be reversible if such treatment is stopped, the child or young person will have missed a period, however long, of normal biological, psychological and social experience through adolescence; and that missed development and experience, during adolescence, can never be truly be recovered or "reversed".

66. It is to be noted that prior to June 2020, the NHS website on PBs said:

> "The effects of treatment with GnRH analogues are considered to be fully reversible, so treatment can usually be stopped at any time."

67. In June 2020 this section was updated to read as follows:

> "**Little is known about the long-term side effects of hormone or puberty blockers in children with gender dysphoria.**
>
> Although the Gender Identity Development Service (GIDS) advises that is a physically reversible treatment if stopped, **it is not known what the psychological effects may be.**

> **It's also not known whether hormone blockers affect the development of the teenage brain or children's bones**. Side effects may also include hot flushes, fatigue and mood alterations." (emphasis added)

68. A second key part of the argument about reversibility turns on the relationship between PBs and CSH and the degree to which commencing PBs in practice puts a young person on a virtually inexorable path to taking CSH. CSH are to a very significant degree not reversible. As is set out above at para 57 above, a very high proportion of those who start PBs move on to CSH and thus in statistical terms once a child or young person starts on PBs they are on a very clear clinical pathway to CSH.

Evidence base to support the use of Puberty Blockers for Gender Dysphoria

69. The claimants submit that the treatment of PBs for GD is properly described as (i) experimental (ii) a treatment with a very limited evidence base, and (iii) as a highly controversial treatment. The claimants rely on witness statements from a number of undoubted experts in various relevant fields and from academic institutions in the United Kingdom, the USA, Sweden and Australia who refer to the controversial nature of the treatment and its limited evidential support.

70. It is not however the court's role to judge the weight to be given to various different experts in a judicial review. In our view, more important is the evidence from the defendant and the evidence base *it* relies upon for the use of PBs. In the USA the treatment of GD is not an FDA approved use and as such PBs can only be used "off-label". That does not prevent clinicians, whether in the USA or the United Kingdom, from using PBs for this purpose, as long as their use falls within the clinician's professional expertise. Professor Butler explained that it is very common for paediatric medicines to be used off-label and that this factor does not render the treatment in any sense experimental.

71. However, the lack of a firm evidence base for their use is evident from the very limited published material as to the effectiveness of the treatment, however it is measured.

72. Paul Jenkins, Chief Executive of the defendant said:

> "…it is correct that in recent years, some clinicians [at the Trust] have raised their concerns about the use of GnRHa for young people presenting with gender dysphoria. Indeed, some have called for the Trust to alter its practices and have done so in a variety of ways. We are keenly aware that the subject of gender dysphoria raises complex issues and that many have strong opinions about it."

73. The Evaluation Paper on the Early Intervention Study at GIDS, referred to in para 25 above, gives some (albeit limited) material on the outcome of that study. It summarised a meeting paper presented by Dr Carmichael and Professor Viner in 2014 (but not published in a peer review journal) as follows:

> "The reported qualitative data on early outcomes of 44 young people who received early pubertal suppression. It noted that 100% of young people stated that they wished to continue on GnRHa, that 23 (52%) reported an improvement in mood since starting the blocker but that 27% reported a decrease in mood. **Noted that there was no overall improvement in mood or psychological wellbeing using standardized psychological measures**." (emphasis added)

74. Ms Morris submitted it is not for this court to determine clinical disagreements between experts about the efficacy of a treatment. We agree. That is a matter for the relevant NHS and regulatory bodies to oversee and to decide. However the degree to which the treatment is experimental and has, as yet, an unknown impact, does go to the critical issue of whether a young person can have sufficient understanding of the risks and benefits to be able lawfully to consent to that treatment.

Persistence

75. The claimants submit that there is good evidence that for a significant proportion of young people presenting with GD, the condition resolves itself through adolescence without treatment with PBs. Further, that PBs serve to increase the likelihood of GD, and, as such, can be positively harmful to the child or young person's long-term health. According to DSM5: "*in natal males, persistence of [gender dysphoria] has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%."* These figures need to be treated with some caution because it may be that the cohort whose persistence was being considered in these statistics was at a lower age and with less clearly established GD than the young people being treated at GIDS.

76. The Dutch study argued that adolescents who show established GD rarely identify as their biological sex. Professor Hruz suggested there may be two reasons for this. It may be that the clinicians made sound diagnoses of persistent GD. Alternatively, it may be that the very fact of the diagnosis and the course of treatment which affirmed that diagnosis (that is, both gender affirmative psychotherapy and the use of PBs) solidified the feeling of cross-gender identification and led the young people to commit to sex reassignment more strongly than they would have done if there had been a different diagnosis and treatment.

77. As already indicated, it is not our role to adjudicate on the reasons for persistence or otherwise of GD. However, the nature of this issue highlights the highly complex and unusual nature of this treatment and the great difficulty there is in fully understanding its implications for the individual young person. In short, the treatment may be supporting the persistence of GD in circumstances in which it is at least possible that without that treatment, the GD would resolve itself.

SECTION B: EVIDENCE OF THE CLAIMANTS AND OTHER INDIVIDUALS

78. The first claimant was born a female. In her witness statement in these proceedings she set out her experience of being prescribed PBs and then CSH. It should be noted that some of the details relating to her treatment and the information she was given (at GIDS and the first defendant) is disputed. This case is a judicial review of the GIDS policy,

not a tort action relating to the specific facts surrounding the first claimant's treatment and it is not necessary therefore to resolve any factual dispute. We simply record the first claimant's account. She describes a highly traumatic childhood. From the age of 4 or 5 she displayed gender non-conformity, associating more with male games and clothes. She felt highly alienated at secondary school and took birth control pills to stop her periods. She felt disgusted by her body and became depressed and highly anxious. From the age of 14 she began actively to question her gender identity and started to look at YouTube videos and do research on the internet about gender identity disorder and the transition process. She said: "*I thought I had finally found the answer as to why I felt so masculine, uncomfortable with my female body and why I was so much more similar to a stereotypical boy than to a stereotypical girl in physical expression and interests."*

79. When she was 15, the first claimant was referred to GIDS. When she was at the local Children and Adolescent Mental Health Services clinic she remembered: *"the psychiatrist attempted to talk of the gender spectrum as a way of persuading me to not pursue medical transition. I took this as a challenge to how serious I was about my feelings and what I wanted to do and it made me want to transition more. Now I wish I had listened to her."* She was first seen at GIDS aged 16 and had a number of appointments spread out over 1 year and 9 months. She was referred to UCLH in June 2013 and after three appointments commenced PBs. She was given advice about the impact on her fertility, but her priority was to move on to testosterone. She said that at 16, she was not thinking about children and, in any event, egg storage was not available on the NHS.

80. In April 2014 she was referred to an adult Gender Identity Clinic to discuss surgery. She "*was visualising myself becoming a tall, physically strong young man where there was virtually no difference between me and a biological boy."* After commencing testosterone at 17, changes to her body commenced rapidly: these changes included genital changes, her voice dropping and the growth of facial and body hair. She was on testosterone for 3 years but increasingly began to doubt the process of transition:

> "27. I started to have my first serious doubts about transition. These doubts were brought on by for the first time really noticing how physically different I am to men as a biological female, despite having testosterone running through my body. There were also a lot of experiences I could not relate to when having conversations with men due to being biologically female and socialised in society as a girl. There was an unspoken "code" a lot of the time that I felt I was missing. I remember telling a close male friend at the time about these transition doubts, who responded by telling me that I was being silly and I believed him. This was reinforced by the online forums that I browsed where the consensus was that most transsexual people have doubts and that that is a normal part of transitioning, so the doubts should be ignored. I continued on, pushing the doubts in the far back of my mind and no more doubts creeped in for a while."

81. Despite these doubts, when she was 20, she had a double mastectomy. In the year following this:

> "31. … I started to realise that the vision I had as a teenager of becoming male was strictly a fantasy and that it was not possible. My biological make-up was still female and it showed, no matter how much testosterone was in my system or how much I would go to the gym. I was being perceived as a man by society, but it was not enough. I started to just see a woman with a beard, which is what I was. I felt like a fraud and I began to feel more lost, isolated and confused than I did when I was pre-transition."

82. She described facing the reality of taking a regular dose of drugs for the rest of her life to maintain her male appearance; and the need to have a hysterectomy if she remained a man because of the atrophy of her reproductive organs if she continued to take testosterone.

83. From January 2019 the first claimant stopped taking testosterone. She now wishes to identify as a woman and is seeking to change her legal sex back to that on her original birth certificate. She said:

> "39. … It is only until recently that I have started to think about having children and if that is ever a possibility, I have to live with the fact that I will not be able to breastfeed my children. I still do not believe that I have fully processed the surgical procedure that I had to remove my breasts and how major it really was. I made a brash decision as a teenager, (as a lot of teenagers do) trying to find confidence and happiness, except now the rest of my life will be negatively affected. I cannot reverse any of the physical, mental or legal changes that I went through. Transition was a very temporary, superficial fix for a very complex identity issue."

84. The defendant submits the first claimant was given the fullest possible information after a large number of consultations (at least 10) and that she was *Gillick* competent to make the decision to take PBs. Further, the defendant produced witness statements from a number of children and young people who are strongly supportive of the treatment they have received.

85. J is a 20 year old transgender man who received PBs in 2012 at the age of 12 followed by CSH in 2015. He described how he felt a strong need to become a boy from an early age and how he was bullied at school for his behaviour. He found the onset of female puberty horrifying and unbearable. After a number of sessions at GIDS he was prescribed PBs from the age of 12.

86. According to J he was given the fullest possible information from the clinicians at GIDS as to the benefits and disbenefits of the treatment. The clinicians strongly challenged his desire to transition and why he had chosen to express his gender identity as male. He was advised as to the impact on fertility if he chose to go on to CSH and surgery. He said: "*I made the decision to proceed with pubertal suppression without pursuing egg preservation. It was a difficult decision to make because I did not know whether I would want biological children in adulthood, but I was certain I would never want to*

carry a child and give birth. Ultimately, I made the decision because I had a poor quality of life and without immediate treatment I did not feel I had a future at all." He says: "*We discussed sex and I told them the idea of it disgusted me. I knew I would be unable to consider having a sexual relationship as an adult with my body so wrongly formed."* He ended his witness statement by saying that he is thankful that his pubertal development was halted as it removed the distress caused by continued development, but he wishes that the PBs were started earlier which would have prevented the need for breast surgery later.

87. S is a 13 year old trans boy who is on the waiting list at GIDS. He was told that he would have to wait for approximately 24 months to be seen and with his parents decided to see a private provider, GenderGP, where he has been prescribed PBs. We note at this point that the GP in question was removed from the professional register and now operates from outside the United Kingdom. S in his witness statement said:

> "13. … I haven't really thought about parenthood – I have been asked about it by the gender identity specialist I have mentioned but I just have no idea what me in the future is going to think. I haven't had a romantic relationship and it's just not a thing that is really on my radar at the moment."

88. N, an 18 year old trans woman, who was prescribed PBs when she was 17 years old said:

> "12. The treatment of hormone blockers may very well have saved my life. In the period of my life that I was prescribed them my mental health was spiralling due to my dysphoria and this impacting on my daily life, learning and social interactions. While the first injections of gonapeptyl were slow to take effect they eventually began to alleviate my dysphoria in very real ways. I had to shave less and I didn't have to fear pubertal development anymore. I had the time necessary to think about my situation and decide on further courses of action. This also helped my mental health as it gave me significantly less issues overall allowing me to focus and concentrate on aspects in my life alongside my gender identity rather than my fears of puberty and development overtaking everything else in my life."

89. The second claimant, Mrs A, is the mother of a 15 year old girl who has ASD. The daughter has a history of mental health and behavioural problems. She "*is desperate to run away from all that made her female"* and has been referred to CAMHS (Child and Adolescent Mental Health Services). Mrs A is very concerned that her daughter would be referred to GIDS and prescribed PBs. However the daughter has not currently been referred to GIDS and having regard to the defendant's current practice, would not meet the criteria for PBs because her parents would not support that treatment. Mrs A's interest in this action is therefore largely theoretical.

SECTION C: SUBMISSIONS

90. The claimants' primary case is that children or young persons under the age of 18 are not capable of giving consent to the administration of PBs. Their secondary case is that the information given by the defendant and the Interested Party is misleading and inadequate to form the basis for informed consent to be given. In their statement of issues, the claimants put issue one as the adequacy of the information and issue two whether children and young people are capable of giving consent. In our view, the first issue must be whether *Gillick* competence can be achieved, and the secondary or alternative issue, whether the information being given is adequate. We deal with the arguments in that order.

91. Mr Hyam also raised a third issue (at least in writing). This was a submission that if any young person under the age of 18 is prescribed PBs, their case should be referred to the Court of Protection. In oral argument he accepted that the Court of Protection, being a creature of statute, would have no jurisdiction to consider such referrals. We think that the substance of issue three falls within the terms of issue one.

92. Mr Hyam stressed that the claimants were not calling into question that GD existed. Nor were they questioning that it could cause extreme distress or that PBs should never be given to people under 18 or that it was never in their best interests for it to be prescribed. The central issue was whether those under 18 could give informed consent.

93. Mr Hyam submitted that a child still going through puberty is not capable of properly understanding the nature and effect of PBs and weighing the consequences and side effects properly. He pointed to the evidence of the individuals, including that put forward on behalf of the defendant, to show that children of this age cannot understand the implications of matters such as the loss of the ability to orgasm, the potential need to construct a neo-vagina, or the loss of fertility. He argued that the use of PBs to address GD does not have an adequate evidence base to support it and thus should properly be described as experimental treatment. There is evidence that PBs can have significant side effects and there is strong evidence that once a child commences on PBs they will progress to CSH which will cause irreversible changes to the child's body with lifelong medical, psychological and emotional implications for the child. He relies on the harm potentially caused to these vulnerable young people as evidenced by the witness statement of the first claimant.

94. He submitted that the advice given to the children and young persons is misleading because they are told that the PBs are fully reversible when the current evidence on reversibility or the long term implications of the treatment is limited and unclear. He said further, that the reality is that PBs pave the way for CSH which do have irreversible impacts. Further, the information provided by GIDS fails to tell the child that there are no proven benefits to this treatment in either physical or psychological terms. The information is misleading as to the reversibility of PBs, their purpose and their benefits.

95. In those circumstances he submitted that the court should be guided by the approach of the Court of Protection in its *Practice Guidance (Court of Protection: Serious Medical Treatment)* [2020] 1 WLR 641 which sets out those decisions relating to medical treatment where an application should be made to the Court of Protection.

96. Paras 10 and 11 of that Guidance state:

> "10. In any case which is not about the provision of life-sustaining treatment, but involves the serious interference with the person's rights under the ECHR, it is:
>
> "highly probable that, in most, if not all, professionals faced with a decision whether to take that step will conclude that it is appropriate to apply to the court to facilitate a comprehensive analysis of [capacity and] best interests, with [the person] having the benefit of legal representation and independent expert advice."
>
> This will be so even where there is agreement between all those with an interest in the person's welfare.
>
> 11. Examples of cases which may fall into paragraph 10 above will include, but are not limited to: (a) where a medical procedure or treatment is for the primary purpose of sterilisation; (b) where a medical procedure is proposed to be performed on a person who lacks capacity to consent to it, where the procedure is for the purpose of a donation of an organ, bone marrow, stem cells, tissue or bodily fluid to another person; (c) a procedure for the covert insertion of a contraceptive device or other means of contraception; (d) where it is proposed that an experimental or innovative treatment to be carried out; (e) a case involving a significant ethical question in an untested or controversial area of medicine."

97. The defendant and the first and second Interveners make common cause. Ms Morris argued that the care and treatment provided at GIDS fell within the terms of the Service Specification laid down by NHS England (NHSE) as required in accordance with the international frameworks of WPATH and the Endocrine Society and by the domestic regulatory frameworks of the General Medical Council and the Care Quality Commission. The NHSE is currently undertaking a review of the efficacy of treatment for GD (the Cass Review) which will report in due course, and its findings will be reflected in the Service Specification.

98. She argued that the process at GIDS was "deeply *Montgomery* compliant" (i.e. it met the requirements for informed consent identified by the Supreme Court in *Montgomery v Lanarkshire Health Board* [2015] AC 1430) having regard to the frequent consultations, discussions and the provision of detailed, but age appropriate, information. The "vast majority" of the children referred for PBs are 15 or older she said, and the information given is varied depending on the age and maturity of the child or young person. Where the assessment is that the individual is not initially *Gillick* competent, time is taken to see if their understanding develops and competency can be achieved. The information that is given is what is salient for that individual at that age.

99. As to those between the ages of 16-18, if the young person, the parents and the clinicians are agreed then she submitted there is no justiciable issue and the court has no jurisdiction.

100. Mr McKendrick for the first and second Interveners argued that the child or young person did not need to understand the impact of CSH on their fertility because that did

not fall to be decided at the stage of prescribing PBs. The PBs provided the space for the person to think about further stages. In appropriate cases, a natal girl or young person's eggs could be harvested and preserved in order to preserve their fertility. The critical thing for the child was that s/he had GD and that there was no alternative physical treatment to PBs. Once the child or young person had reached the Endocrine Clinic at the Trust, there was no alternative psychological treatment available because that was a matter within the purview of GIDS and GIDS had referred the child for PBs, although ongoing psychological treatment is provided at GIDS alongside treatment with PBs. Therefore, the Trust clinicians were faced with a child in acute distress with no alternative treatment options. The purpose of the treatment was to alleviate distress and that, according to Mr McKendrick, had been achieved.

101. When asked by the court what evidence there was that the PBs did achieve the purpose of alleviating distress, in the light of the lack of published research, Mr McKendrick pointed to the evidence of experienced endocrinologists in both Trusts who could see the real benefits of the treatment.

102. Like Ms Morris, Mr McKendrick said the current practice was not to proceed only on parental consent. However, he did argue that if the child's consent was rendered invalid, the treatment would continue to be lawful if the parents had consented.

103. The third Intervener is Transgender Trend Ltd., an organisation that provides evidence-based information and resources for parents and schools concerning children with GD. Ms Davies-Arai is the director of that organisation and she has filed a witness statement in these proceedings. She set out concerns about the lack of evidence as to the impacts and effectiveness of PBs and in relation to which patients it is most likely to help. Much of her evidence focused on the increase of referrals to GIDS of teenage natal girls and the cultural factors, including material on the internet and social media, which may play a part in this. She said that GIDS does not offer young people with GD a range of ways to interpret their experience, and the GIDS pathway offers a minimal challenge to the beliefs and ideas of the young person.

104. Mr Skinner on behalf of Transgender Trend said the case was particularly important because it concerned the deliberate provision by the State of medical treatment to children and young people which may cause harm. The court should be anxious to ensure that vulnerable children, for example those with ASD, are provided with the full protection of the law.

SECTION D: THE LAW

105. In *Gillick v West Norfolk and Wisbech Health Authority* [1986] AC 112, the House of Lords considered the lawfulness of the Secretary of State's policy on giving contraceptive advice to children without parental consent. The House of Lords held by a majority that a doctor could lawfully give contraceptive advice and treatment to a girl aged under 16 if she had sufficient maturity and intelligence to understand that nature and implications of the proposed treatment and provided that certain conditions were satisfied.

106. Lord Fraser at p. 169B-E said:

> "It seems to me verging on the absurd to suggest that a girl or boy aged 15 could not effectively consent, for example, to have a medical examination of some trivial injury to his body or even to have a broken arm set. Of course the consent of the parents should normally be asked, but they may not be immediately available. Provided the patient, whether the boy or a girl, is capable of understanding what is proposed, and of expressing his or her own wishes, I see no good reason for holding that he or she lacks the capacity to express them validly and effectively and to authorise the medical man to make the examination or give the treatment which he advises. After all, a minor under the age of 16 can, with certain limits, enter into a contract. He or she can also sue and be sued, and can give evidence on oath. …."
>
> Accordingly, I am not disposed to hold now, for the first time, that a girl less than 16 lacks the power to give valid consent to contraceptive advice or treatment, merely on account of her age."

107. Lord Scarman at p. 186A-D said:

> "The law relating to parent and child is concerned with the problems of the growth and maturity of the human personality. If the law should impose upon the process of "growing up" fixed limits where nature knows only a continuous process, the price would be artificiality and a lack of realism in an area where the law must be sensitive to human development and social change. If certainty be thought desirable, it is better that the rigid demarcations necessary to achieve it should be laid down by legislation after a full consideration of all the relevant factors than by the courts confined as they are by the forensic process to the evidenced adduced by the parties and to whatever may properly fall within the judicial notice of judges. Unless and until Parliament should think fit to intervene, the courts should establish a principle flexible enough to enable justice to be achieved by its application to the particular circumstances proved by the evidence placed before them."

And at p.189C-E:

> "When applying these conclusions to contraceptive advice and treatment it has to be borne in mind there is much that has to be understood by a girl under the age of 16 if she is to have legal capacity to consent to such treatment. It is not enough that she should understand the nature of the advice which is being given: she must also have a sufficient maturity to understand what is involved. There are moral and family questions, especially her relationship with her parents; long-term problems associated with the emotional impact of pregnancy and its termination; and there are the risks to health of sexual intercourse at her age, risks which contraception may diminish but cannot eliminate. It follows that a doctor will have to satisfy himself that she is able to appraise these factors

> before he can safely proceed upon the basis that she has at law capacity to consent to contraceptive treatment. And it further follows that ordinarily the proper course will be for him, as the guidance lays down, first to seek to persuade the girl to bring her parents into consultation and, if she refuses, not to prescribe contraceptive treatment unless he is satisfied that her circumstances are such that he ought to proceed without parental knowledge and consent."

And p. 191C-D:

> "The truth may well be that the rights of parents and children in this sensitive area are better protected by the professional standards of the medical profession than by "a priori" legal lines of division between capacity and the lack of capacity to consent since any such general dividing line is sure to produce in some cases injustice, hardship, and injury to health."

108. In *R (Axon) v Secretary of State for Health (Family Planning Association Intervening)* [2006] QB 539 Silber J considered *Gillick* in the context of Article 8 of the Convention, the United Nations Convention on the Rights of the Child (UNCRC) and the increasing emphasis on the autonomy of the child. He held that the principles set out in *Gillick* continued to apply, see para 152.

109. There are two cases dealing with children aged 16 or over who refused medical treatment in circumstances where clinicians considered it was clinically indicated. The issue in each was whether the court could nevertheless, authorise the treatment. *Re W (a Minor) (Medical Treatment: Court's Jurisdiction)* [1993] Fam. 64, concerned the case of a 16 year old girl with anorexia nervosa. The local authority applied under the inherent jurisdiction of the High Court to give medical treatment to W without her consent and against her wishes. W relied on section 8 of the Family Law Reform Act 1969, which states:

> "Section 8 is in these terms:
>
> (1) The consent of a minor who has attained the age of 16 years to any surgical, medical or dental treatment which, in the absence of consent, would constitute a trespass to his person, shall be as effective as it would be if he were of full age; and where a minor has by virtue of this section given an effective consent to any treatment it shall not be necessary to obtain any consent for it from his parent or guardian. (2) In this section 'surgical, medical or dental treatment' includes any procedure undertaken for the purposes of diagnosis, and this section applies to any procedure which is ancillary to any treatment as it applies to that treatment. (3) Nothing in this section shall be construed

> as making ineffective any consent which would have been effective if this section had not been enacted."

110. The Court of Appeal held that section 8 did not confer on a minor an absolute right to determine whether or not she received medical treatment but protected the medical practitioner from an action in trespass. Lord Donaldson analysed *Gillick* and said that Lord Scarman would necessarily have considered that the purpose of section 8 was to provide the medical practitioners treating the child with a defence to either criminal assault or a civil claim for trespass, see pages 76G-H and 78D-F. Lord Donaldson described the effect of the section as being a *"legal flak jacket",* whereby the 16-17 year old is conclusively proved to be *Gillick* competent but this did not mean that someone else who has parental responsibility cannot give consent for the treatment.

111. When applying his analysis to the facts of W's case, Lord Donaldson said at p. 80G-81B:

> "I have no doubt that the wishes of a 16 or 17-year-old child or indeed of a younger child who is "Gillick competent" are of the greatest importance both legally and clinically, but I do doubt whether Thorpe J was right to conclude that W was of sufficient understanding to make an informed decision. I do not say this on the basis that I consider her approach irrational. I personally consider that religious or other beliefs which bar any medical treatment or treatment of particular kinds are irrational, but that does not make minors who hold those beliefs any the less "Gillick competent". They may well have sufficient intelligence and understanding fully to appreciate the treatment proposed and the consequences of their refusal to accept that treatment. What distinguishes W from them, and what with all respect I do not think that Thorpe J took sufficiently into account (perhaps because the point did not emerge as clearly before him as it did before us), is that it is a feature of anorexia nervosa that it is capable of destroying the ability to make an informed choice. It creates a compulsion to refuse treatment or only to accept treatment which is likely to be ineffective. This attitude is part and parcel of the disease and the more advanced the illness, the more compelling it may become. Where the wishes of the minor are themselves something which the doctors reasonably consider need to be treated in the minor's own best interests, those wishes clearly have a much reduced significance."

112. Lord Donaldson concluded at p. 84A-B that:

> "No minor of whatever age has power by refusing consent to treatment to override a consent to treatment by someone who has parental responsibility for the minor and a fortiori a consent by the court. Nevertheless such a refusal is a very important consideration in making clinical judgments and for parents and the courts in deciding whether themselves to give consent. Its importance increases with the age and maturity of the minor."

113. Balcombe LJ at p. 87G-H agreed with Lord Donaldson that the parents of a 16 and 17 year old retained the right to consent to treatment even if she did not consent, and that the court could continue to exercise its inherent jurisdiction. Nolan LJ did not express a view as to whether parents could consent to treatment where the child had refused, but considered that the court under its inherent jurisdiction could continue to do so. He said, at p. 94D-E:

> "To take it a stage further, if the child's welfare is threatened by a serious or imminent risk that the child will suffer grave and irreversible mental or physical harm, then once again the court when called upon has a duty to intervene. It makes no difference whether the risk arises from the action or inaction of others, or from the action or inaction of the child. Due weight must be given to the child's wishes, but the court is not bound by them. In the present case, Thorpe J was apparently satisfied on the evidence before him that such a risk existed. In my judgment, he was fully entitled to take this view. By the time the matter came to this court, it was impossible to take any other view. For these reasons, I would dismiss the appeal save to the extent of making the necessary variation of the order of Thorpe J."

114. We were taken to two cases concerning the application of *Gillick* in particularly difficult medical and ethical situations, which are of some assistance in the present case. In *Re L (Medical Treatment: Gillick Competency*) [1998] 2 F.L.R. 810 Sir Stephen Brown P. considered the case of a 14 year old girl with a life threatening condition involving the possibility of a blood transfusion. L was a Jehovah's Witness and would not consent to the blood transfusion. The court ordered that the medical treatment should take place without her consent. The expert clinician appointed by the Official Solicitor is recorded as giving the following evidence:

> "He makes the point that the girl's view as to having no blood transfusion is based on a very sincerely, strongly held religious belief which does not in fact lend itself in her mind to discussion. It is one that has been formed by her in the context of her own family experience and the Jehovah's Witness meetings where they all support this view. He makes the point that there is a distinction between a view of this kind and the constructive formulation of an opinion which occurs with adult experience. That has not happened of course in the case of this young girl."

115. Sir Stephen Brown then concluded at p. 813:

> "It is, therefore, a limited experience of life which she has – inevitably so – but this is in no sense a criticism of her or of her upbringing. It is indeed refreshing to hear of children being brought up with the sensible disciplines of a well-conducted family. But it does necessarily limit her understanding of matters which are as grave as her own present situation. It may be that because of her belief she is willing to say, and to mean it, 'I am willing to accept death rather than to have a blood transfusion', but it is quite clear in this case that she has not been able to be given all the

> details which it would be right and appropriate to have in mind when making such a decision.
>
> I do not think that in this case this young girl is 'Gillick competent'. I base that upon all the evidence that I have heard. She is certainly not 'Gillick competent' in the context of all the necessary details which it would be appropriate for her to be able to form a view about."

116. *Re S (A Child) (Child Parent: Adoption Consent)* [2019] 2 Fam 177 also concerned a child under 16. In that case Cobb J considered the competence of a mother under the age of 16 to consent to her baby being placed for adoption. Cobb J held that it was appropriate and helpful in determining *Gillick* competence to read across and borrow from the relevant concepts and language in the Mental Capacity Act 2005 but cognisant of some fundamental differences, in particular that the assumption of capacity in section 1(2) of that Act did not apply and there was no requirement for any diagnostic characteristic as there is in section 2(1) of the Mental Capacity Act 2005, see paras 15,16 and 60.

117. At paras 34 to 37 Cobb J considered what test he should apply to the information that S needed to understand and then set out the information that would be relevant for the decision in question:

> "34. Macur J in *LBL v RYJ and VJ* [2011] 1 FLR 1279, para 24 held that it would not be necessary for a decision-maker to be able to comprehend "all the peripheral detail" in the assessment of capacity to make the relevant decision; in a case concerning residence and the provision of education, Macur J went on to say, at para 58:
>
> "In [the expert's] view it is unnecessary for his determination of RYJ's capacity that she should understand all the details within the statement of special educational needs. It is unnecessary that she should be able to give weight to every consideration that would otherwise be utilised in formulating a decision objectively in her 'best interests'. I agree with his interpretation of the test in section 3 which is to the effect that the person under review must comprehend and weigh the salient details relevant to the decision to be made. To hold otherwise would place greater demands upon RYJ than others of her chronological age/commensurate maturity and unchallenged capacity."
>
> 35. In the same vein, Baker J remarked in *H v A Local Authority* [2011] EWHC 1704 at [16(xi)]: "[the] courts must guard against imposing too high a test of capacity to decide issues such as residence because to do so would run the risk of discriminating against persons suffering from a mental disability."
>
> 36. Although not cited in argument, I further remind myself of the comments of Chadwick LJ in the Court of Appeal in *Masterman-Lister v Brutton & Co (Nos 1 and 2)* [2003] 1 WLR 1511, para 79: "a person should not be held unable to understand the information relevant to a

decision if he can understand the explanation of that information in broad terms and simple language…" So, says Ms Dolan, it is not necessary for S to understand all the peripheral and non-salient information in the adoption consent form in order to be declared capacitous. Nor does she even need to fully understand the legal distinctions between placement for adoption under a placement order and not under a placement order. Indeed, Ms Dolan herself relies in this regard on *In re A (Adoption: Agreement: Procedure)* [2001] 2 FLR 455, para 43 where Thorpe LJ observes that the differences between freeing and adoption are "complex in their inter-relationship and it is not to be expected that social workers should have a complete grasp of the distinction between the two, or always to signify the distinction in their discussion with the clients" (my emphasis)." If social workers are not expected to understand the complexities of the legislation (or its predecessor) or explain the distinction accurately to the parents with whom they are working asks Ms Dolan, why should a person under the age of 16 be expected to be able to grasp them in order to be able to be declared capacitous?

37. Accordingly, argues the local authority, the salient or "sufficient" information which is required to be understood by the child parent regarding extra-familial adoption is limited to the fundamental legal consequences of the same. The factors discussed at the hearing include: (i) your child will have new legal parents, and will no longer be your son or daughter in law, (ii) adoption is final, and non-reversible; (iii) during the process, other people (including social workers from the adoption agency) will be making decisions for the child, including who can see the child, and with whom the child will live; (iv) you may obtain legal advice if you wish before taking the decision; (v) the child will live with a different family forever; you will (probably) not be able to choose the adopters; (vi) you will have no right to see your child or have contact with your child; it is highly likely that direct contact with your child will cease, and any indirect contact will be limited; (vii) the child may later trace you, but contact will only be re-established if the child wants this; (viii) there are generally two stages to adoption; the child being placed with another family for adoption, and being formally adopted; (ix) for a limited period of time you may change your mind; once placed for adoption, your right to change your mind is limited, and is lost when an adoption order is made."

118. Cobb J's conclusions were these:

"60… It follows that in order to satisfy the Gillick test in this context the child parent should be able to demonstrate "sufficient" understanding of the "salient" facts around adoption; she should understand the essential "nature and quality of the transaction" (per Munby J in *Sheffield City Council v E* [2005] Fam 326, para 19) and should not need to be concerned with the peripheral.

> 61. It will, however, be necessary for the competent child decision-maker to demonstrate a "full understanding" of the essential implications of adoption when exercising her decision-making, for the independent CAFCASS officer to be satisfied that the consent is valid. If consent is offered under section 19 and/or section 20 of the 2002 Act, it will be necessary for a form to be signed, even if not in the precise format of that identified by Practice Direction 5A. I accept that on an issue as significant and life-changing as adoption, there is a greater onus on ensuring that the child understands and is able to weigh the information than if the decision was of a lesser magnitude: see Baker J in *CC v KK and STCC* [2012] COPLR 627, para 69. This view is consistent with the Mental Capacity Act 2005 Code of Practice, which provides, at paragraph 4.19:
>
> "a person might need more detailed information or access to advice, depending on the decision that needs to be made. If a decision could have serious or grave consequences, it is even more important that a person understands the information relevant to that decision.""

119. In determining the level of understanding that the child needs to have to consent to PBs, Mr Hyam attached considerable importance to the decision of the Supreme Court in *Montgomery v Lancashire Health Board*. That case concerned an action in negligence brought by a mother on behalf of her child. The child was disabled as a result of complications during delivery and the mother argued that she should have been advised as to the possibility of delivery by elective caesarean. The central issue for present purposes was the information that the doctor needed to have given the patient in order to establish that she had given informed consent for the treatment.

120. Lord Kerr set out the requirements placed on a doctor in providing information on risks of injury from treatment in the following terms at para 87:

> "An adult person of sound mind is entitled to decide which, if any, of the available forms of treatment to undergo, and her consent must be obtained before treatment interfering with her bodily integrity is undertaken. The doctor is therefore under a duty to take reasonable care to ensure that the patient is aware of any material risks involved in any recommended treatment, and of any reasonable alternative or variant treatments. The test of materiality is whether, in the circumstances of the particular case, a reasonable person in the patient's position would be likely to attach significance to the risk, or the doctor is or should reasonably be aware that the particular patient would be likely to attach significance to it."

121. Mr Hyam submitted that in determining whether a child is *Gillick* competent the court should consider what would a *"reasonable person in the patient's position understand",* and in asking that question, he submitted that the "reasonable person" is one with adult knowledge.

122. Ms Morris went to the opposite extreme. She submitted that when deciding what information needs to be given to the patient and understood by them, the test is a reasonable person in that individual's position, i.e. a reasonable 12 year old (or other

age) with GD. She said that the "salient" information that needs to be provided is what that reasonable patient would attach importance to. She said that seeking consent, certainly for treatment with lifelong implications such as sterilisation will always involve some *"act of imagination"*. Many patients facing life changing treatment, such as the loss of fertility in cancer treatment or endometriosis, will not have had experience of what they are foregoing, for example, fertility. She submitted that the court ought not to be pronouncing on hypothetical cases: rather, it should or could consider the facts of one specific case as and when it arises.

123. Mr McKendrick submitted that the correct approach in deciding what information was material was to assume a reasonable child of the individual's age.

124. Mr Skinner pointed out that *Montgomery* concerned an adult and therefore the presumption of capacity in the Mental Capacity Act 2005 applied. That presumption is inapplicable in a case concerning *Gillick* competency where the very issue is whether the child is competent to make the decision. The decision in *Montgomery* was of limited assistance, therefore, in the present case. In determining competence, the child must have sufficient understanding of the factors that are not just relevant to him or her now but which on an objective basis ought to be given weight in the future.

125. In our view, the following principles can be derived from the cases to which we have referred:

126. First, the question as to whether a person under the age of 16 is *Gillick* competent to make the relevant decision will depend on the nature of the treatment proposed as well as that person's individual characteristics. The assessment is necessarily an individual one. Where the decision is significant and life changing then there is a greater onus to ensure that the child understands and is able to weigh the information, see *Re S* at para 60.

127. Secondly, however, that does not mean that it is not possible for the court to draw some lines. The Trusts themselves accept that a 7 year old being treated with PBs for precocious puberty cannot give informed consent and his or her parents must give that consent because of the young age of the child concerned and the nature of the treatment.

128. Thirdly, efforts should be made to allow the child or young person to achieve *Gillick* competency where that is possible. Clinicians should therefore work with the individual to help them understand the treatment proposed and its potential implications in order to help them achieve competence.

129. Fourthly, however, that does not mean that every individual under 16 can achieve *Gillick* competence in relation to the treatment proposed. As we discuss below, where the consequences of the treatment are profound, the benefits unclear and the long-term consequences to a material degree unknown, it may be that *Gillick* competence cannot be achieved, however much information and supportive discussion is undertaken.

130. Fifthly, in order to achieve *Gillick* competence it is important not to set the bar too high. It is not appropriate to equate the matters that a clinician needs to explain, as set out in *Montgomery*, to the matters that a child needs to understand to achieve *Gillick* competence. The consequence of Mr Hyam's approach would be significantly to raise

the bar for competence and capacity, which would be contrary both to the common law and to a child's Article 8 rights and the importance of supporting individual autonomy.

131. We adopt the language of Chadwick LJ in *Masterman-Lister v Brutton and Co (Nos 1 and 2)* [2003] 1 WLR 151: a person should be able to "*understand an explanation of that information in broad terms and simple language"*, see *Re S* at para 36. Although this was said in a case that concerned an adult's capacity, in our judgment the same approach should be applied to a case concerning *Gillick* competence. The child or young person needs to be able to demonstrate sufficient understanding of the salient facts, see *Re S* at para 60.

132. Sixthly, we agree with Mr Skinner, that in deciding what facts are salient and what level of understanding is sufficient, it is necessary to have regard to matters which are those which objectively ought to be given weight in the future although the child might be unconcerned about them now. On the facts of this case there are some obvious examples, including the impact on fertility and on future sexual functioning.

SECTION E: CONCLUSIONS

133. The principal issue before this court is in some ways a narrow one. Can a child or young person under the age of 16 achieve *Gillick* competence in respect of the decision to take PBs for GD? The legal position of 16 and 17 year olds is different, and we deal with that below.

134. The starting point is to consider the nature of the treatment proposed. The administration of PBs to people going through puberty is a very unusual treatment for the following reasons. Firstly, there is real uncertainty over the short and long-term consequences of the treatment with very limited evidence as to its efficacy, or indeed quite what it is seeking to achieve. This means it is, in our view, properly described as experimental treatment. Secondly, there is a lack of clarity over the purpose of the treatment: in particular, whether it provides a "pause to think" in a "hormone neutral" state or is a treatment to limit the effects of puberty, and thus the need for greater surgical and chemical intervention later, as referred to in the Health Research Authority report. Thirdly, the consequences of the treatment are highly complex and potentially lifelong and life changing in the most fundamental way imaginable. The treatment goes to the heart of an individual's identity, and is thus, quite possibly, unique as a medical treatment.

135. Furthermore, the nature and the purpose of the medical intervention must be considered. The condition being treated, GD, has no direct physical manifestation. In contrast, the treatment provided for that condition has direct physical consequences, as the medication is intended to and does prevent the physical changes that would otherwise occur within the body, in particular by stopping the biological and physical development that would otherwise take place at that age. There is also an issue as to whether GD is properly categorised as a psychological condition, as the DSM-5 appears to do, although we recognise there are those who would not wish to see the condition categorised in that way. Be that as it may, in our judgment for the reasons already identified, the clinical intervention we are concerned with here is different in kind to other treatments or clinical interventions. In other cases, medical treatment is used to remedy, or alleviate the symptoms of, a diagnosed physical or mental condition, and

the effects of that treatment are direct and usually apparent. The position in relation to puberty blockers would not seem to reflect that description.

136. Indeed the consequences which flow from taking PBs for GD and which must be considered in the context of informed consent, fall into two (interlinking) categories. Those that are a direct result of taking the PBs themselves, and those that follow on from progression to Stage 2, that is taking cross-sex hormones. The defendant and the Trusts argue that Stage 1 and 2 are entirely separate; a child can stop taking PBs at any time and that Stage 1 is fully reversible. It is said therefore the child needs only to understand the implications of taking PBs alone to be *Gillick* competent. In our view this does not reflect the reality. The evidence shows that the vast majority of children who take PBs move on to take cross-sex hormones, that Stages 1 and 2 are two stages of one clinical pathway and once on that pathway it is extremely rare for a child to get off it.

137. The defendant argues that PBs give the child "time to think", that is, to decide whether or not to proceed to cross-sex hormones or to revert to development in the natal sex. But the use of puberty blockers is not itself a neutral process by which time stands still for the child on PBs, whether physically or psychologically. PBs prevent the child going through puberty in the normal biological process. As a minimum it seems to us that this means that the child is not undergoing the physical and consequential psychological changes which would contribute to the understanding of a person's identity. There is an argument that for some children at least, this may confirm the child's chosen gender identity at the time they begin the use of puberty blockers and to that extent, confirm their GD and increase the likelihood of some children moving on to cross-sex hormones. Indeed, the statistical correlation between the use of puberty blockers and cross-sex hormones supports the case that it is appropriate to view PBs as a stepping stone to cross-sex hormones.

138. It follows that to achieve *Gillick* competence the child or young person would have to understand not simply the implications of taking PBs but those of progressing to cross-sex hormones. The relevant information therefore that a child would have to understand, retain and weigh up in order to have the requisite competence in relation to PBs, would be as follows: (i) the immediate consequences of the treatment in physical and psychological terms; (ii) the fact that the vast majority of patients taking PBs go on to CSH and therefore that s/he is on a pathway to much greater medical interventions; (iii) the relationship between taking CSH and subsequent surgery, with the implications of such surgery; (iv) the fact that CSH may well lead to a loss of fertility; (v) the impact of CSH on sexual function; (vi) the impact that taking this step on this treatment pathway may have on future and life-long relationships; (vii) the unknown physical consequences of taking PBs; and (viii) the fact that the evidence base for this treatment is as yet highly uncertain.

139. It will obviously be difficult for a child under 16 to understand and weigh up such information. Although a child may understand the concept of the loss of fertility for example, this is not the same as understanding how this will affect their adult life. A child's attitude to having biological children and their understanding of what this really means, is likely to change between childhood and adulthood. For many children, certainly younger children, and some as young as 10 and just entering puberty, it will not be possible to conceptualise what not being able to give birth to children (or conceive children with their own sperm) would mean in adult life. Similarly, the

meaning of sexual fulfilment, and what the implications of treatment may be for this in the future, will be impossible for many children to comprehend.

140. Ms Morris submitted that many decisions about complex and long-lasting medical treatment will involve the patient having, to some degree, to imagine themselves into an uncertain future of which they have no experience. However, for the reasons that we have explained in para 135 above we consider the treatment in this case to be in entirely different territory from the type of medical treatment which is normally being considered.

141. Some of the children and young people who have been treated at GIDS say in their witness statements that the thought of sex disgusted them, or they did not really think about fertility. These normal reactions do not detract from the difficulties surrounding consent and treatment with PBs. That adolescents find it difficult to contemplate or comprehend what their life will be like as adults and that they do not always consider the longer-term consequences of their actions is perhaps a statement of the obvious.

142. These various difficulties are compounded by the particular difficulties prevalent in the cohort of children treated at GIDS. On the defendant's case, they suffer considerable psychological distress by reason of their GD and are highly vulnerable. In those circumstances, the consequences of taking PBs on their fertility for example, or on their sexual life, may be viewed as a relatively small price to pay for what may be perceived as a solution to their immediate and real psychological distress. It would not follow however that their weighing of risks and benefits when they might start taking PBs would prevail in the longer-term.

143. The difficulty of achieving informed consent in these circumstances is further exacerbated by the lack of evidence as to the efficacy of PBs in treating GD and the long-term outcomes of taking it. We entirely accept that the fact that a treatment is experimental, or that the long-term outcomes are not yet known, does not of itself prevent informed consent being given. Otherwise no experimental treatment could ever be consented to. However, the combination here of lifelong and life changing treatment being given to children, with very limited knowledge of the degree to which it will or will not benefit them, is one that gives significant grounds for concern.

144. We do not think that the answer to this case is simply to give the child more, and more detailed, information. The issue in our view is that in many cases, however much information the child is given as to long-term consequences, s/he will not be able to weigh up the implications of the treatment to a sufficient degree. There is no age appropriate way to explain to many of these children what losing their fertility or full sexual function may mean to them in later years.

145. *Gillick* makes clear that any decision is treatment and person specific. However, for the reasons that we have set out above, we think that it is appropriate in this case to give clear guidance as to the application of the *Gillick* tests to the treatment and cohort of children in question. The conclusion we have reached is that it is highly unlikely that a child aged 13 or under would ever be *Gillick* competent to give consent to being treated with PBs. In respect of children aged 14 and 15, we are also very doubtful that a child of this age could understand the long-term risks and consequences of treatment in such a way as to have sufficient understanding to give consent. However, plainly the

increased maturity of the child means that there is more possibility of achieving competence at the older age.

146. In respect of a young person aged 16 or over, the legal position is different. There is a presumption of capacity under section 8 of the Family Law Reform Act 1969. As is explained in *Re W*, that does not mean that a court cannot protect the child under its inherent jurisdiction if it considers the treatment not to be in the child's best interests. However, so long as the young person has mental capacity and the clinicians consider the treatment is in his/her best interests, then absent a possible dispute with the parents, the court generally has no role. We do not consider that the court can somehow adopt an intrusive jurisdiction in relation to one form of clinical intervention for which no clear legal basis has been established.

147. We do however recognise that in the light of the evidence that has emerged, and the terms of this judgment, clinicians may well consider that it is not appropriate to move to treatment, such as PBs or CSH, without the involvement of the court. We consider that it would be appropriate for clinicians to involve the court in any case where there may be any doubt as to whether the long-term best interests of a 16 or 17 year old would be served by the clinical interventions at issue in this case.

148. We express that view for these reasons. First, the clinical interventions involve significant, long-term and, in part, potentially irreversible long-term physical, and psychological consequences for young persons. The treatment involved is truly life changing, going as it does to the very heart of an individual's identity. Secondly, at present, it is right to call the treatment experimental or innovative in the sense that there are currently limited studies/evidence of the efficacy or long-term effects of the treatment.

149. The position of the defendant and the Trusts is that they consider it would be an intrusion into the child or young person's autonomy if a decision about treatment with PBs were to be made by the court not by the patient. They are concerned about the use of NHS and court resources if these decisions have to be made by the court. We do not consider that this is the correct approach. In principle, a young person's autonomy should be protected and supported; however, it is the role of the court to protect children, and particularly a vulnerable child's best interests. The decisions in respect of PBs have lifelong and life-changing consequences for the children. Apart perhaps from life-saving treatment, there will be no more profound medical decisions for children than whether to start on this treatment pathway. In those circumstances we consider that it is appropriate that the court should determine whether it is in the child's best interests to take PBs. There is a real benefit in the court, almost certainly with a child's guardian appointed, having oversight over the decision. In any case, under the inherent jurisdiction concerning medical treatment for those under the age of 18, there is likely to be a conflict between the support of autonomy and the protective role of the court. As we have explained above, we consider this treatment to be one where the protective role of the court is appropriate.

150. The claimants' alternative ground is that the information provided by the defendant and the Trusts is inadequate to form the basis of informed consent. We accept that the defendant and the Trusts have in their written information, to children, young people and their parents and carers, tried hard to explain the potential consequences of PBs, including that of moving on to CSH, and to give full information. They have also

attempted to do this in an age appropriate manner. The problem is not the information given, but the ability of the children and young people, to understand and most importantly weigh up that information. The approach of the defendant appears to have been to work on the assumption that if they give enough information and discuss it sufficiently often with the children, they will be able to achieve *Gillick* competency. As we have explained above, we do not think that this assumption is correct.

OVERALL CONCLUSION

151. A child under 16 may only consent to the use of medication intended to suppress puberty where he or she is competent to understand the nature of the treatment. That includes an understanding of the immediate and long-term consequences of the treatment, the limited evidence available as to its efficacy or purpose, the fact that the vast majority of patients proceed to the use of cross-sex hormones, and its potential life changing consequences for a child. There will be enormous difficulties in a child under 16 understanding and weighing up this information and deciding whether to consent to the use of puberty blocking medication. It is highly unlikely that a child aged 13 or under would be competent to give consent to the administration of puberty blockers. It is doubtful that a child aged 14 or 15 could understand and weigh the long-term risks and consequences of the administration of puberty blockers.

152. In respect of young persons aged 16 and over, the legal position is that there is a presumption that they have the ability to consent to medical treatment. Given the long-term consequences of the clinical interventions at issue in this case, and given that the treatment is as yet innovative and experimental, we recognise that clinicians may well regard these as cases where the authorisation of the court should be sought prior to commencing the clinical treatment.

153. We have granted a declaration to reflect the terms of this judgment.