No. 23-12155

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

August Dekker et al.,
Plaintiffs-Appellees,

v.

Secretary, Florida Agency for Health Care Administration et al.,
Defendants-Appellants.

U.S. District Court for the Northern District of Florida, No. 4:22-cv-325
(Hinkle, J.)

APPELLANTS' APPENDIX – VOLUME XX OF XXI
PART 1 OF 2

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Dated: October 13, 2023

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Study	QUALITY					Summary of findings				IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision		No of events/No of patients% (n/N%)		Effect			
						Intervention	Comparator	Result			
								Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of treatment.			

Other safety outcomes: adverse effects

Proportion of patients reporting adverse effects

Study	Risk of bias	Indirectness	Inconsistency	Imprecision		Intervention	Comparator	Result		IMPORTANCE	CERTAINTY
1 cohort study Khatchado urian 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

Study	QUALITY					Summary of findings				IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision		No of events/No of patients (n/N%)		Effect			
						Sex assigned at birth males	Sex assigned at birth females	Result			

Subgroups: sex assigned at birth males compared with sex assigned at birth females

This document was prepared in October 2020

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients (n/N%)		Effect		
					Sex assigned at birth males	Sex assigned at birth females	Result		

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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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

This document was prepared in October 2020

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		

Mean [±SD] Trait Anxiety (STAI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
	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).

This document was prepared in October 2020

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients (n/N%) — Sex assigned at birth males	Sex assigned at birth females	Effect — 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 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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Effect — Result	IMPORTANCE	CERTAINTY
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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Effect — Result	IMPORTANCE	CERTAINTY
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.

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Effect — Result	IMPORTANCE	CERTAINTY
1 cohort study Costa et al 2015	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	n=not reported	n=not reported	t-test 2.15; $P=0.03$[5]	Important	VERY LOW

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients (n/N%)		Effect		
					Sex assigned at birth males	Sex assigned at birth females	Result		
					55.4 [±12.7]	59.2 [±11.8]			

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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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 [±10.57]	n-NR[7] score at T0 61.73 [±13.60] score at T1 57.73 [±10.82]	F-ratio 2.64 (*df, errdf*: 1,52), *P=0.110*	Important	VERY LOW

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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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).

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients (n/N%)		Effect		
					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[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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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

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).

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result	IMPORTANCE	CERTAINTY
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).

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients (n/N%)		Effect		
					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[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.

This document was prepared in October 2020

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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Doc. 193-12

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.

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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).

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[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?

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(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

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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) • Testosterone (transmales) Doses and formulations not reported	**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
		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 Retrospective chart review Single centre, Tampere, Finland	52 adolescents with gender dysphoria: 11 transfemales and 41 transmales. Mean age at diagnosis 18.1 years (range 15.2 to 19.9)	**Intervention** Hormonal sex assignment treatment – details of intervention not reported, although all patients received gender-affirming hormones.	**Critical Outcomes** *Impact on mental health* • Need for mental health treatment **Important Outcomes** *Psychosocial Impact* Measure of functioning in different domains of

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Study	Population	Intervention and comparison	Outcomes reported
		Comparison No comparison group. Comparison over time reported	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. Mean age at start of gender-affirming hormones: • Transfemale – 16.4 years (SD 1.1) • Transmale – 16.9 years (SD 1.9)	**Intervention** Oral oestrogen or intramuscular (IM) testosterone **Comparison** No comparison group. Comparison over time reported	**Critical Outcomes** *None reported* **Important Outcomes** *Safety* • Body mass index (BMI) • Systolic blood pressure • Diastolic blood pressure • Glucose • Insulin • HOMA-IR

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Study	Population	Intervention and comparison	Outcomes reported
			• 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 Single centre, Texas, USA	Children and adolescents with gender dysphoria (9 to18 years), n=148, of whom: • 25 received puberty suppression only • 93 received gender-affirming hormone therapy only • 30 received both Mean age 14.9 years	**Intervention** Gender-affirming hormones, guided by Endocrine Society Clinical Practice Guidelines **Comparison** No comparison group. Comparison over time reported.	**Critical Outcomes** *Impact on mental health* • Depression- Quick Inventory of Depressive Symptoms (QIDS), self-reported • Depression- QIDS, clinician-reported • Anxiety- Screen for Child Anxiety Related Emotional Disorders (SCARED)

Study	Population	Intervention and comparison	Outcomes reported
			• 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) **Comparison** No comparison group. Comparison over time reported.	**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, Spanish Version (SDQ-Cas).
Stoffers et al. 2019 Retrospective chart review	62 transmales with gender dysphoria. Patients had received a GnRH analogue and more than 6 months of testosterone treatment.	**Intervention** Testosterone intramuscular injections (Sustanon 250 mg). Dose was titrated to a	**Critical Outcomes** None **Important Outcomes** *Safety*

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Study	Population	Intervention and comparison	Outcomes reported
Single centre, Leiden, Netherlands	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	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.	• 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

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	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	This is a critical outcome because anxiety may impact on social, occupational, or other areas of functioning in children and adolescents.

Certainty of evidence: very low	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 **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, 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 **Certainty of evidence: very low**	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. 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) **Certainty of evidence: very low**	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 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

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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?

Outcome	Evidence statement
Diagnostic criteria	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.**
Age when gender-affirming hormones started	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):

Study	Mean age (± SD)
Allen et al. 2019	16.7 years (not reported)
Khatchadourian et al. 2014	17.4 years (1.9)
Klaver et al. 2020	16.4 years (1.1) in transfemales 16.9 years (0.9) in transmales
Kuper et al. 2020	16.2 (1.2)
Klink et al. 2015	16.6 years (1.4) in transfemales 16.4 years (2.3) in transmales

Study	Median age (range)
Stoffers et al. 2019	17.2 years (15 to 19.5)
Vlot et al. 2017	16.3 years (15.9 to 19.5) in transfemales 16.0 years (14.0 to 18.9) in transmales

	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.**
Duration of treatment with GnRH analogues	The duration of treatment with GnRH analogues was reported in 3/10 studies: **Table continued below**

Study	Median duration
Klaver et al. 2020	2.1 years (IQR 1.0 to 2.7) in transfemales 1.0 years (IQR 0.5 to 2.9) in transmales
Klink et al. 2015	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)
Stoffers et al. 2019	8 months (range 3 to 39)

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.

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:
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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:
----
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:
----
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:
----
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:
----
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)

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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
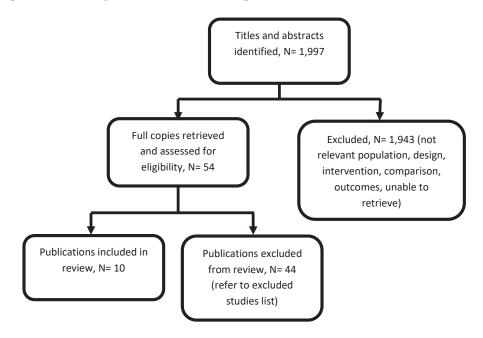   89530
#18   MeSH descriptor: [Child] explode all trees   44089
#19   MeSH descriptor: [Child Behavior] explode all trees 2061
#20   MeSH descriptor: [Child Health] this term only   98
#21   MeSH descriptor: [Child Welfare] this term only   325
#22   MeSH descriptor: [Minors] this term only   8
#23   (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

This document was prepared in October 2020   Page 68 of 156

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.

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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 participants at baseline and 6% (3/50) 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) 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, details of these is not

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	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*	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 Psychology 7(3): 302-311	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-affirming hormones for	39 participants received gender-affirming hormones only 8 participants received a GnRH analogue followed by gender-affirming hormones. Mean duration of treatment in the gender-	**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
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.	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 received a GnRH	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
	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 a year on gender-affirming hormones.	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 assessment and 6% (3/52) needed treatment during the 12-month 'real life'	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
Study dates 2011 to 2017	the ICD-10 is 'transsexualism'. Mean age at diagnosis 18.1 years (range 15.2 to 19.9)		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, reported over the approximately 12-month period after starting gender-affirming	Other comments: None Source of funding: No source of funding reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			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)	
			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:
			  o 2 transmales due to concomitant mental health comorbidities
			  o 1 transmale due to androgenic alopecia.
			  o 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
				
				Other comments: Mental health comorbidity was reported for all participants but not for the gender-affirming hormone cohort separately.

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: o 7 transmales had severe acne (requiring isotretinoin) o 1 transmale had andogenic alopecia o 3 transmales had mild dyslipidaemia (levels not reported) o 1 transmale had significant mood swings o No transfemales had minor complications	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 **Study type**	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 within 1.5 years before or after the 22nd birthday), iii) if	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/m² 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 22 years= 23.2, 95% CI 21.6 to 24.8). At age 22 years, 9.9% of the cohort were	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
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	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.	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 decreased (mean change -0.5, 95% CI -

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			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)

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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/m³ • 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/m³ • 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

This document was prepared in October 2020

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/m² • 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/m² • 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/m³ • Start of gender-affirming hormones: 0.26 (0.04) • Age 22 years: 0.28 (0.05) • No statistically significant difference z-score (SD)	concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• 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) • P<0.001 z-score (SD)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• 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, age at initial assessment, and	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 Manual of Mental Disorders, Fifth Edition criteria for gender	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 follow-up. The authors did not present statistical analysis for the sub-group of participants receiving gender-affirming	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
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.	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.		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 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-	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

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

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.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			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	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	Gender-affirming hormones- • Oral oestradiol • Intramuscular testosterone Participants had previously received gonadotropin-releasing	**Critical Outcomes** ***Impact on gender dysphoria*** Following gender-affirming hormones for 12 months, mean (±SD) Utrecht Gender Dysphoria Scale (UGDS) score statistically	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

This document was prepared in October 2020

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
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	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	hormone (GnRH) analogues in the intermediate pubertal stages (Tanner 2–-3).	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 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	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** Other comments: None Source of funding: Not reported

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			months after gender-affirming hormones (10.3 points; SD±2.9; p<0.001) *No other critical or important outcomes 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/cm²: • 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/cm²:

- 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/cm²:

- 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 testosterone treatment to 6, 12 and

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

			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 group had a bone age of	**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	<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. Median (range), g/m^3	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• 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)	

This document was prepared in October 2020

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				
					No of patients		Effect	IMPORTANCE	CERTAINTY
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				
					No of events		Effect	IMPORTANCE	CERTAINTY
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 | | | |
| | | | | | No of events | | Effect | IMPORTANCE | CERTAINTY |
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

CERTIFICATE OF SERVICE

I certify that I e-filed this appendix on ECF, which will email everyone requiring

notice.

Dated: October 13, 2023   /s/ Mohammad O. Jazil

No. 23-12155

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

August Dekker et al.,
Plaintiffs-Appellees,

v.

Secretary, Florida Agency for Health Care Administration et al.,
Defendants-Appellants.

U.S. District Court for the Northern District of Florida, No. 4:22-cv-325
(Hinkle, J.)

APPELLANTS' APPENDIX – VOLUME XX OF XXI
PART 2 OF 2

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Dated: October 13, 2023

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Study	QUALITY				No of events		Effect	IMPORTANCE	CERTAINTY
	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)

Study	QUALITY				No of events		Effect	IMPORTANCE	CERTAINTY
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.

Study	QUALITY				No of events		Effect	IMPORTANCE	CERTAINTY
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.

Study	QUALITY				No of events		Effect	IMPORTANCE	CERTAINTY
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.

Study	QUALITY				No of events		Effect	IMPORTANCE	CERTAINTY
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

| Study | QUALITY | | | | No of events | | Summary of findings | IMPORTANCE | CERTAINTY |
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect (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

Study	QUALITY				No of events		Summary of findings		IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect			
								Result		

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.

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	IMPORTANCE	CERTAINTY
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	who received gender-affirming hormones 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 |

This document was prepared in October 2020

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events		Effect		
					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				
							No of events		Effect	
Study	Risk of bias	Indirectness	Inconsistency	Imprecision			Intervention	Comparator	Result	IMPORTANCE	CERTAINTY

Need for mental health treatment, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	IMPORTANCE	CERTAINTY
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	4% (2/52) Statistically significant reduction (p<0.001) 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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	IMPORTANCE	CERTAINTY
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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result	IMPORTANCE	CERTAINTY
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)

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	QUALITY				No of events		Summary of findings Effect	IMPORTANCE	CERTAINTY
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)

	QUALITY				No of events		Summary of findings Effect	IMPORTANCE	CERTAINTY
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)

	QUALITY				No of events		Summary of findings Effect	IMPORTANCE	CERTAINTY
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)

	QUALITY				No of events		Summary of findings Effect	IMPORTANCE	CERTAINTY
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

This document was prepared in October 2020

Study	QUALITY					Summary of findings				IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision			No of events		Effect		
						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; 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

Study	QUALITY					Summary of findings				IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision			No of patients		Effect		
						Intervention	Comparator	Result			
Impact on quality of life (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)											

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Study	QUALITY				Summary of findings				
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect	IMPORTANCE	CERTAINTY
					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

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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.

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect	Importance	Certainty
					Intervention	Comparator	Result		
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

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					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

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Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — 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.

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)		
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 |

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Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					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)

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
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).

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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

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect		
							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/m³ 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/m³ Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24)	Important	VERY LOW

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Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					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)

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	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=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

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Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — 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/m³ — 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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)	IMPORTANCE	CERTAINTY
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/m³ — 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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)	IMPORTANCE	CERTAINTY
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m³	Important	VERY LOW

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Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					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

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
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/m³ 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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/m³ C0: 0.27 (0.20 to 0.33) C24: 0.27 (0.20 to 0.36)	Important	VERY LOW

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Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					Intervention	Comparator	Result (95% CI)		
							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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/m³ 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

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
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/m³ 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)

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — 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 ($p \leq 0.01$) z-score (range) C0: -0.37 (-2.28 to 0.47) C24: -0.37 (-2.03 to 0.85) Statistically significant increase ($p \leq 0.01$)	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)

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
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 ($p \leq 0.01$) z-score (range) C0: -0.27 ((-1.91 to 1.29) C24: 0.02 (-2.1 to 1.35) Statistically significant increase ($p \leq 0.05$)	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

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
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

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Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transmales

Study	QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect			
					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			
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/m² 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)

Study	QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect			
					Intervention	Comparator	Result (95% CI)			
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/cm² 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

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Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — 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

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)	IMPORTANCE	CERTAINTY
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/m² 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

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)	IMPORTANCE	CERTAINTY
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/m² 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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)	IMPORTANCE	CERTAINTY
1 cohort study	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6)	None	Mean (SD), g/cm² T0: 0.77 (0.08)	Important	VERY LOW

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Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					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)

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					Intervention	Comparator	Result (95% CI)		
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

Study	QUALITY					No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision		Intervention	Comparator	Effect		
								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

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Study	QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect			
					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										

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Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — 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 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

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Study	QUALITY				No of patients		Summary of findings — Effect	IMPORTANCE	CERTAINTY
	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

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
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.

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
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

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
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

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Study	QUALITY				No of patients		Summary of findings		IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect	Result (95% CI)		

Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transmales

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect	IMPORTANCE	CERTAINTY
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean glucose level at 22 years (95% CI): 4.8 (4.7 to 5.0) 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.

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect	IMPORTANCE	CERTAINTY
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)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect	IMPORTANCE	CERTAINTY
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

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Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect		
							Result (95% CI)		
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
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transfemales									

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Study	QUALITY				No of patients		Summary of findings Effect	IMPORTANCE	CERTAINTY
	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): +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

Study	QUALITY				No of patients		Effect	IMPORTANCE	CERTAINTY
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

Study	QUALITY				No of patients		Effect	IMPORTANCE	CERTAINTY
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

Study	QUALITY				No of patients		Effect	IMPORTANCE	CERTAINTY
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)	Important	VERY LOW

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	QUALITY				No of patients		Summary of findings — Effect	IMPORTANCE	CERTAINTY
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 transmales

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)	IMPORTANCE	CERTAINTY
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean LDL cholesterol at 22 years (95% CI): 2.6 (2.4 to 2.8) — 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				No of patients		Summary of findings — Effect	IMPORTANCE	CERTAINTY
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		

Liver enzymes (1 uncontrolled, retrospective observational study)

Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)

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| Study | QUALITY | | | | No of patients | | Summary of findings | IMPORTANCE | CERTAINTY |
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect Result (95% CI)		
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) N-15 (T24)	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) Statistically significant increase from T0 at T6 and T12 ($p<0.001$)	Important	VERY LOW

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Study	QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect			
					Intervention	Comparator		Result (95% CI)		

Kidney markers (1 uncontrolled, retrospective observational study)

Change from start of testosterone in serum creatinine level in transmales (up to 24 months follow-up)

Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect	IMPORTANCE	CERTAINTY
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 Khatchado urian 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 Khatchado urian et al. 2014 | Serious limitations[3] | No serious indirectness | Not applicable | Not calculable | N=63 | None | 3/37 transmales receiving testosterone temporarily discontinued treatment, 2 due to concomitant mental health | Important | VERY LOW |

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Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					Intervention	Comparator	Result (95% CI)		
Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchado urian 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. comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment. No transfemales receiving oestrogen temporarily discontinued treatment	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 Khatchado urian 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

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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

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Effect — 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) **Transmales** T0 (baseline) = 64.95 (SE 2.66)	Critical	VERY LOW

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Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Effect		
							Result (95% CI)		
							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)

Study type and number of studies Author year	QUALITY				No of events/No of patients% (n/N%)		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect		
							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 Kuper et al. 2020	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) No statistical analysis reported for this sub-group	Critical	VERY LOW

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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.

Study type and number of studies, Author year	QUALITY				No of events/No of patients% (n/N%)		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect Result (95% CI)		
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 |

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.

Study type and number of studies Author year	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of events/No of patients% (n/N%)		Effect		
					Intervention	Comparator	Result (95% CI)		
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)

This document was prepared in October 2020

| Study | QUALITY | | | | No of patients | | Summary of findings | | IMPORTANCE | CERTAINTY |
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect	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
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	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)		Critical	VERY LOW

Study	QUALITY					Summary of findings				
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		IMPORTANCE	CERTAINTY
					Intervention	Comparator	Result (95% CI)			
Kuper et al. 2020							No statistical analysis reported for this sub-group			
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

| Study | QUALITY | | | | No of patients | | Effect | IMPORTANCE | CERTAINTY |
	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
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

Study	QUALITY				Summary of findings			IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	No of patients		Effect		
					Intervention	Comparator	Result (95% CI)		
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									
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	Important	VERY LOW

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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

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)		
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	No statistically significant difference p=0.06 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

Study	QUALITY				No of patients		Summary of findings	IMPORTANCE	CERTAINTY
	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Effect — Result (95% CI)		
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).

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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. 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	VERY LOW

This document was prepared in October 2020

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).

This document was prepared in October 2020

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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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

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[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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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.

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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

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Doc. 193-16

Standards of Care for the Health of Transgender and Gender Diverse People, Version 8

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ABSTRACT

Background: Transgender healthcare is a rapidly evolving interdisciplinary field. In the last decade, there has been an unprecedented increase in the number and visibility of transgender and gender diverse (TGD) people seeking support and gender-affirming medical treatment in parallel with a significant rise in the scientific literature in this area. The World Professional Association for Transgender Health (WPATH) is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. One of the main functions of WPATH is to promote the highest standards of health care for TGD people through the Standards of Care (SOC). The SOC was initially developed in 1979 and the last version (SOC-7) was published in 2012. In view of the increasing scientific evidence, WPATH commissioned a new version of the Standards of Care, the SOC-8.

Aim: The overall goal of SOC-8 is to provide health care professionals (HCPs) with clinical guidance to assist TGD people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment.

Methods: The SOC-8 is based on the best available science and expert professional consensus in transgender health. International professionals and stakeholders were selected to serve on the SOC-8 committee. Recommendation statements were developed based on data derived from independent systematic literature reviews, where available, background reviews and expert opinions. Grading of recommendations was based on the available evidence supporting interventions, a discussion of risks and harms, as well as the feasibility and acceptability within different contexts and country settings.

Results: A total of 18 chapters were developed as part of the SOC-8. They contain recommendations for health care professionals who provide care and treatment for TGD people. Each of the recommendations is followed by explanatory text with relevant references. General areas related to transgender health are covered in the chapters Terminology, Global Applicability, Population Estimates, and Education. The chapters developed for the diverse population of TGD people include Assessment of Adults, Adolescents, Children, Nonbinary, Eunuchs, and Intersex Individuals, and people living in Institutional Environments. Finally, the chapters related to gender-affirming treatment are Hormone Therapy, Surgery and Postoperative Care, Voice and Communication, Primary Care, Reproductive Health, Sexual Health, and Mental Health.

Conclusions: The SOC-8 guidelines are intended to be flexible to meet the diverse health care needs of TGD people globally. While adaptable, they offer standards for promoting optimal health care and guidance for the treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria set forth in this document for gender-affirming medical interventions are clinical guidelines; individual health care professionals and programs may modify these in consultation with the TGD person.

INTRODUCTION

Purpose and use of the Standards of Care

The overall goal of the World Professional Association for Transgender Health's (WPATH) Standards of Care—Eighth Edition (SOC-8) is to provide clinical guidance to health care professionals to assist transgender and gender diverse (TGD) people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment. This assistance may include but is not limited to hormonal and surgical treatments, voice and communication therapy, primary care, hair removal, reproductive and sexual health, and mental health care. Healthcare systems should provide medically necessary gender-affirming health care for TGD people: See Chapter 2—Global Applicability, Statement 2.1.

WPATH is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. Founded in 1979, the organization currently has over 3,000 health care professionals, social scientists, and legal professionals, all of whom are engaged in clinical practice, research, education and advocacy that affects the lives of TGD people. WPATH envisions a world wherein people of all gender identities and gender expressions have access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the Standards of Care (SOC) for the health of TGD people. The SOC-8 is based on the best available science and expert professional consensus. The SOC was initially developed in 1979, and the last version was published in 2012.

Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC-8 to other parts of the world are necessary. Suggestions for approaches to cultural relativity and cultural competence are included in this version of the SOC.

WPATH recognizes that health is not only dependent upon high-quality clinical care but also relies on social and political climates that ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that advance tolerance and equity for gender diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these policy and legal changes. Thus, health care professionals who provide care to TGD people are called upon to advocate for improved access to safe and licensed gender-affirming care while respecting the autonomy of individuals.

While this is primarily a document for health care professionals, individuals, their families, and social institutions may also use the SOC-8 to understand how it can assist with promoting optimal health for members of this diverse population.

The SOC-8 has 18 chapters containing recommendations for health care professionals working with TGD people. Each of the recommendations is followed by explanatory text with relevant references. The recommendations for the initiation of gender-affirming medical and/or surgical treatments (GAMSTs) for adults and adolescents are contained in their respective chapters (see Assessment for Adults and Adolescent chapters). A summary of the recommendations and criteria for GAMST can be found in Appendix D.

Populations included in the SOC-8

In this document, we use the phrase transgender and gender diverse (TGD) to be as broad and comprehensive as possible in describing members of the many varied communities that exist globally of people with gender identities or expressions that differ from the gender socially attributed to the sex assigned to them at birth. This includes people who have culturally specific and/or language-specific experiences, identities or expressions, which may or may not be based on or encompassed by Western conceptualizations of gender or the language used to describe it.

WPATH SOC-8 expands who is included under the TGD umbrella, and the settings in which these guidelines should be applied to promote equity and human rights.

Globally, TGD people encompass a diverse array of gender identities and expressions and have differing needs for gender-affirming care across their lifespan that is related to individual goals and characteristics, available health care resources, and sociocultural and political contexts. When standards of care are absent for certain groups this vacuum can result in a multiplicity of therapeutic approaches, including those that may be counterproductive or harmful. The SOC-8 includes recommendations to promote health and well-being for gender diverse groups that have often been neglected and/or marginalized, including nonbinary people, eunuch, and intersex individuals.

The SOC-8 continues to outline the appropriate care of TGD youth, which includes, when indicated, the use of puberty suppression and, when indicated, the use of gender-affirming hormones.

Worldwide, TGD people commonly experience transphobia, stigmatization, ignorance, and refusal of care when seeking health care services, which contributes to significant health disparities. TGD people often report having to teach their medical providers how to care for them due to the latter's insufficient knowledge and training. Intersectional forms of discrimination, social marginalization, and hate crimes against TGD people lead to minority stress. Minority stress is associated with mental health disparities exemplified by increased rates of depression, suicidality, and non-suicidal self-injuries than rates in cisgender populations. Professionals from every discipline should consider the marked vulnerability of many TGD people. WPATH urges health care authorities, policymakers, and medical societies to discourage and combat transphobia among health care professionals and ensure every effort is made to refer TGD people to professionals with experience and willingness to provide gender-affirming care.

Flexibility in the SOC

The SOC-8 guidelines are intended to be flexible to meet the diverse health care needs of TGD people globally. While adaptable, they offer standards for promoting optimal health care and for guiding treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria put forth in this document for gender-affirming interventions are clinical guidelines; individual health care professionals and programs may modify them in consultation with the TGD person. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health care professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

The SOC-8 supports the role of informed decision-making and the value of harm reduction approaches. In addition, this version of the SOC recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Health care professionals can use the SOC to help patients consider the full range of health services open to them in accordance with their clinical needs for gender expression.

Diversity versus Diagnosis

The expression of gender characteristics, including identities, that are not stereotypically associated with one's sex assigned at birth is a common and a culturally diverse human phenomenon that should not be seen as inherently negative or pathological. Unfortunately, gender nonconformity and diversity in gender identity and expression is stigmatized in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in "minority stress." Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make TGD individuals more vulnerable to developing mental health concerns such as anxiety and depression. In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and

neglect in one's interpersonal relationships, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being TGD.

While Gender Dysphoria (GD) is still considered a mental health condition in the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5-TR) of the American Psychiatric Association. Gender incongruence is no longer seen as pathological or a mental disorder in the world health community. Gender Incongruence is recognized as a condition in the International Classification of Diseases and Related Health Problems, 11th Version of the World Health Organization (ICD-11). Because of historical and current stigma, TGD people can experience distress or dysphoria that may be addressed with various gender-affirming treatment options. While nomenclature is subject to change and new terminology and classifications may be adopted by various health organizations or administrative bodies, the medical necessity of treatment and care is clearly recognized for the many people who experience dissonance between their sex assigned at birth and their gender identity.

Not all societies, countries, or health care systems require a diagnosis for treatment. However, in some countries these diagnoses may facilitate access to medically necessary health care and can guide further research into effective treatments.

Health care services

The goal of gender-affirming care is to partner with TGD people to holistically address their social, mental, and medical health needs and well-being while respectfully affirming their gender identity. Gender-affirming care supports TGD people across the lifespan—from the very first signs of gender incongruence in childhood through adulthood and into older age—as well as people with concerns and uncertainty about their gender identity, either prior to or after transition.

Transgender health care is greater than the sum of its parts, involving holistic inter- and multidisciplinary care between endocrinology, surgery, voice and communication, primary care, reproductive health, sexual health and mental health disciplines to support gender-affirming interventions as well as preventive care and chronic disease management. Gender-affirming interventions include puberty suppression, hormone therapy, and gender-affirming surgeries among others. It should be emphasized there is no 'one-size-fits-all' approach and TGD people may need to undergo all, some, or none of these interventions to support their gender affirmation. These guidelines encourage the use of a patient-centered care model for initiation of gender- affirming interventions and update many previous requirements to reduce barriers to care.

Ideally, communication and coordination of care should occur between providers to optimize outcomes and the timing of gender-affirming interventions centered on the patient's needs and desires and to minimize harm. In well-resourced settings, multidisciplinary consultation and care coordination is often routine, but many regions worldwide lack facilities dedicated to transgender care. For these regions, if possible, it is strongly recommended that individual care providers create a network to facilitate transgender health care that is not available locally.

Worldwide, TGD people are sometime forced by family members or religious communities to undergo conversion therapy. WPATH strongly recommends against any use of reparative or conversion therapy (see statements 6.5 and 18.10).

Health care settings

The SOC-8 are guidelines rooted in the fundamental rights of TGD people that apply to all settings in which health care is provided regardless of an individual's social or medical circumstances. This includes a recommendation to apply the standards of care for TGD people who are incarcerated or living in other institutional settings.

Due to a lack of knowledgeable providers, untimely access, cost barriers and/or previous stigmatizing health care experiences, many TGD people take non-prescribed hormone therapy. This poses health risks associated with the use of unmonitored therapy in potentially supratherapeutic doses and the potential exposure to blood-borne illnesses if needles are shared for administration. However, for many individuals, it is the only means of acquiring medically necessary

gender-affirming treatment that is otherwise inaccessible. Non-prescribed hormone use should be approached with a harm-reduction lens to ensure individuals are connected with providers who can prescribe safe and monitored hormone therapy.

In some countries, the rights of TGD are increasingly being recognized, and gender clinics are being established that can serve as templates for care. In other countries, however, such facilities are lacking and care may be more fragmented and under-resourced. Nonetheless, different models of care are being pioneered, including efforts to decentralize gender-affirming care within primary care settings and establish telehealth services to reduce barriers and improve access. Regardless of the method of care delivery, the principles of gender-affirming care as outlined in the SOC-8 should be adapted to align with local sociocultural, political, and medical contexts.

Methodology

This version of the Standards of Care (SOC-8) is based upon a more rigorous and methodological evidence-based approach than previous versions. This evidence is not only based on the published literature (direct as well as background evidence) but also on consensus-based expert opinion. Evidence-based guidelines include recommendations intended to optimize patient care that are informed by a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility.

While evidence-based research provides the basis for sound clinical practice guidelines and recommendations, it must be balanced by the realities and feasibility of providing care in diverse settings. The process for development of the SOC-8 incorporated the recommendations on clinical practice guideline development set forth by the National Academies of Medicine and the World Health Organization, which addressed transparency, conflict-of-interest policy, committee composition, and group process.

The SOC-8 guidelines committee was multidisciplinary and consisted of subject matter experts, health care professionals, researchers, and stakeholders with diverse perspectives and geographic

representation. A guideline methodologist assisted with the planning and development of questions and systematic reviews with additional input provided by an international advisory committee and during the public comment period. All committee members completed conflict of interest declarations. Recommendations in the SOC-8 are based on available evidence supporting interventions, a discussion of risks and harms, as well as feasibility and acceptability within different contexts and country settings. Consensus on the final recommendations was attained using the Delphi process that included all members of the guidelines committee and required that recommendation statements were approved by at least 75% of members. A detailed overview of the SOC-8 Methodology is included in Appendix A.

SOC-8 Chapters Summary

The SOC-8 represents a significant advancement from previous versions. Changes in this version are based upon a fundamentally different methodology, significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for TGD people beyond hormone therapy and surgery.

These updated guidelines continue the process started with the SOC-7 in 2011 to broaden in scope and move from a narrow focus on psychological requirements for "diagnosing transgenderism" and medical treatments for alleviation of gender dysphoria to gender-affirming care for the whole person. WPATH SOC-8 expands guidelines specifying who is included under the TGD umbrella, what should and should not be offered with gender-affirming care, and the settings in which these guidelines should be applied to promote equity and human rights.

The SOC-8 has several new chapters such as the Assessment of Adults, Education, Eunuchs, and a Nonbinary chapter. In addition, the chapter for children and adolescents of the SOC-7 has been divided into two different chapters. Overall, the SOC-8 is considerably longer than previous versions and provides a more in-depth introduction and recommendations for health care professionals. A summary of every chapter of the SOC-8 can be found below:

Chapter 1—Terminology

This new chapter lays the framework for language used in the SOC-8 and offers consensually agreed upon recommendations for the use of terminology. The chapter provides (1) terms and definitions, and (2) best practices for utilizing them. This document is accompanied by a glossary (see Appendix B) of common terms and language to provide a framework for use and interpretation of the SOC-8.

Chapter 2—Global Applicability

This chapter references key literature related to development and delivery of health care services, broader advocacy care for TGD people from beyond Western Europe and North America and provides recommendations for adapting and translating the SOC-8 to varied contexts.

Chapter 3—Population Estimates

This chapter updates the population estimates of TGD people in society. Based on the current evidence, this proportion may range from a fraction of a percent to several percentage points depending on the inclusion criteria, age group, and geographic location.

Chapter 4—Education

This new chapter provides a general review of the literature related to education in TGD health care. It offers recommendations at governmental, nongovernmental, institutional and provider levels to increase access to competent, compassionate health care. The intent is to lay the groundwork in the education area and invite a much broader and deeper discussion among educators and health care professionals.

Chapter 5—Assessment of Adults

This new chapter provides guidance on the assessment of TGD adults who are requesting gender-affirming medical and surgical treatments (GAMSTs). It describes and updates the assessment process as part of a patient-centered approach and the criteria that health care professionals may follow in order to recommend GAMSTs to TGD adults.

Chapter 6—Adolescents

This new chapter is dedicated to TGD adolescents, is distinct from the child chapter, and has been created for this 8th edition of the Standards of Care given (1) the exponential growth in adolescent referral rates; (2) the increase in studies available specific to adolescent gender diversity-related care; and (3) the unique developmental and gender-affirming care issues of this age group. This chapter provides recommendations regarding the assessment process of adolescents requiring GAMSTs as well as recommendations when working with TGD youth and their families.

Chapter 7—Children

This new chapter pertains to prepubescent gender diverse children and focuses on developmentally appropriate psychosocial practices and therapeutic approaches.

Chapter 8—Nonbinary

This new chapter in the SOC-8 consists of a broad description of the term nonbinary and its usage from a biopsychosocial, cultural, and intersectional perspective. The need for access to gender-affirming care, specific gender-affirming medical interventions, as well as an appropriate level of support is discussed.

Chapter 9—Eunuchs

This new chapter describes the unique needs of eunuchs, and how the SOC can be applied to this population.

Chapter 10—Intersex

This chapter focuses on the clinical care of intersex individuals. It addresses the evolving terminology, prevalence, and diverse presentations of such individuals and provides recommendations for providing psychosocial and medical care with their evidence-based explanations.

Chapter 11—Institutional Environments

This chapter has been expanded to include both carceral and non-carceral settings and has been built upon the last 3 versions of the SOC. This chapter describes how the SOC-8 can be applied to individuals living in these settings.

Chapter 12—Hormone Therapy

This chapter describes the initiation of gender-affirming hormone therapy, the recommended regimens, screening for health concerns before and during hormone therapy, and specific considerations regarding hormone therapy prior to surgery. It includes an expanded discussion about the safety of gonadotropin releasing hormone (GnRH) agonists in youth, various hormone regimens, monitoring to include the development of potential therapy-related health concerns, and guidance on how hormone providers should collaborate with surgeons.

Chapter 13—Surgery and Postoperative Care

This chapter describes a spectrum of gender-affirming surgical procedures for the diverse and heterogeneous community of individuals who identify as TGD. It provides a discussion about the optimal surgical training in GAS procedures, post-surgical aftercare and follow-up, access to surgery by adults and adolescents, and individually customized surgeries.

Chapter 14—Voice and Communication

This chapter describes professional voice and communication support and interventions that are inclusive of and attentive to all aspects of diversity and no longer limited only to voice feminization and masculinization. Recommendations are now framed as affirming the roles and responsibilities of professionals involved in voice and communication support.

Chapter 15—Primary Care

This chapter discusses the importance of primary care for TGD individuals, including topics of cardiovascular and metabolic health, cancer screening, and primary care systems.

Chapter 16—Reproductive Health

This chapter provides recent data on fertility perspectives and parenthood goals in gender diverse youth and adults, advances in fertility preservation methods (including tissue cryopreservation), guidance regarding preconception and pregnancy care, prenatal counseling, and chest feeding. Contraceptive methods and considerations for TGD individuals are also reviewed.

Chapter 17—Sexual Health

This new chapter acknowledges the profound impact of sexual health on physical and psychological well-being for TGD people. The chapter advocates for sexual functioning, pleasure, and satisfaction to be included in TGD-related care.

Chapter 18—Mental Health

This chapter discusses principles of care for managing mental health conditions in TGD adults and the nexus of mental health care and transition care. Psychotherapy may be beneficial but should not be a requirement for gender-affirming treatment, and conversion treatment should not be offered.

CHAPTER 1 Terminology

This chapter will lay the framework for language used in the SOC-8. It offers recommendations for use of terminology. It provides (1) terms and definitions, and (2) best practices for utilizing them. This document is accompanied by a glossary of common terms and language to provide a framework for use and interpretation of the SOC-8. See Appendix B for glossary.

Terminology

In this document, we use the phrase transgender and gender diverse (TGD) to be as broad and comprehensive as possible in describing members of the many varied communities globally of people with gender identities or expressions that differ from the gender socially attributed to the sex assigned to them at birth. This includes people who have culturally specific and/or language-specific experiences, identities or expressions, and/or that are not based on or encompassed by Western conceptualizations of gender, or the language used to describe it. TGD is used for convenience as a shorthand for transgender and gender diverse.

The decision to use transgender and gender diverse resulted from an active process and was not without controversy. Discussions centered on avoiding over-emphasis on the term transgender, integrating nonbinary gender identities and experiences, recognizing global variations in understandings of gender, avoiding the term gender nonconforming, and recognizing the changing nature of language because what is current now may not be so in coming years. Thus, the term transgender and gender diverse was chosen with the intent to be most inclusive and to highlight the many diverse gender identities, expressions, experiences, and health care needs of TGD people. A Delphi process was used wherein SOC-8 chapter authors were anonymously and iteratively surveyed over several rounds to obtain consensus on terms. The SOC-8 presents standards of care that strive to be applicable to TGD people globally, no matter how a person self-identifies or expresses their gender.

Context

The language selected in this chapter may not be (nor ever could be) comprehensive of every culture and geographic region/locale. Differences and debates over appropriate terms and specific terminologies are common, and no single term can be used without controversy. The goal of this chapter is to be as inclusive as possible and offer a shared vocabulary that is respectful and reflective of varied experiences of TGD people while remaining accessible to health practitioners and providers, and the public, for the purposes of this document. Ultimately, access to transition-related health care should be based on providing adequate information and obtaining informed consent from the individual, and not on what words TGD people, or their service providers, use to describe their identities. Using language and terminology that is respectful and culturally responsive is a basic foundation in the provision of affirming care, as is reducing the stigma and harm experienced by many TGD people seeking health care. It is vital for service providers to discuss with service users what language is most comfortable for them and to use that language whenever possible.

This chapter explains why current terms are being used in preference to others. Rather than use specific terms for medical, legal, and advocacy groups, the aim is to foster a shared language and understanding in the field of TGD health, and the many related fields (e.g., epidemiology, law), in order to optimize the health of transgender and gender diverse people.

Sex, gender, gender identity, and gender expression are used in the English language as descriptors that can apply to all people—those who are TGD, and those who are not. There are complex reasons why very specific language may be the *most* respectful, *most* inclusive, or *most* accepted by global TGD communities, including the presence or absence of words to describe these concepts in languages other than English; the structural relationship between sex and gender; legal landscapes at the local, national, and international levels; and the consequences of historical and present-day stigma that TGD people face.

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Statements of Recommendations

1.1- We recommend health care professionals use culturally relevant language (including terms to describe transgender and gender diverse people) when applying the Standards of Care in different global settings.

1.2- We recommend health care professionals use language in health care settings that uphold the principles of safety, dignity, and respect.

1.3- We recommend health care professionals discuss with transgender and gender diverse people what language or terminology they prefer.

Because at present, the field of TGD health is heavily dominated by the English language, there are two specific problems that constantly arise in setting the context for terminology. The first problem is that words exist in English that do not exist in other languages (e.g., "sex" and "gender" are only represented by one word in Urdu and many other languages). The second problem is that there are words that exist outside of English that do not have a direct translation into English (e.g., *travesti, fa'afafine, hijra, selrata, muxe, kathoey, transpinoy, waria, machi*). Practically, this means the heavy influence of English in this field impacts both what terms are widely used and which people or identities are most represented or validated by those terms. The words used also shape the narratives that contribute to beliefs and perceptions. While in past versions of the Standards of Care, World Professional Association for Transgender Health (WPATH) has used only transgender as a broadly defined umbrella term, version 8 broadens this language to use TGD as the umbrella term throughout the document (see Chapter 2—Global Applicability).

Furthermore, the ever-evolving nature of language is impacted by external factors and the social, structural, and personal pressures and violence enacted on TGD people and their bodies. Many of the terms and phrases used historically have been marred by how, when, and why they were used in discussing TGD people, and have thus fallen out of use or are hotly contested among TGD people, with some individuals preferring terms others find offensive. Some wish that these Standards of Care could provide a coherent set of universally accepted terms to describe TGD people, identities, and related health services. Such a list, however, does not and cannot exist without exclusion of some people and without reinforcing structural oppressions, with regards to race,

national origin, Indigenous status, socioeconomic status, religion, language(s) spoken, and ethnicity, among other intersectionalities. It is very likely that at least some of the terminology used in SOC-8 will be outdated by the time version 9 is developed. Some people will be frustrated by this reality, but it is hoped it will be seen instead as an opportunity for individuals and communities to develop and refine their own lexicons and for people to develop a still more nuanced understanding of the lives and needs of TGD people, including TGD people's resilience and resistance to oppression.

Finally, law and the work of legal professionals are within the remit of these Standards of Care. As such, language used most widely in international law is included here to help with the development of the functional definitions of these terms and encourage their usage in legal contexts in lieu of more antiquated and/or offensive terms. The currently most thorough document in international human rights law uses the term "gender diverse."[1]

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 1.1

We recommend health care professionals use culturally relevant language (including terms to describe transgender and gender diverse people) when applying the Standards of Care in different global settings.

Culturally relevant language is used to describe TGD people in different global settings. For example, the concepts of sex, gender, and gender diversity differ across contexts, as does the language used to describe them. Thus, the language used when caring

for TGD people in Thailand is not going to be the same as that used for TGD care in Nigeria. When applying the Standards of Care globally, we recommend health care professionals (HCPs) utilize local language and terms to deliver care in their specific cultural and/or geographical locale.

Gender affirmation refers to the process of recognizing or affirming TGD people in their gender identity—whether socially, medically, legally, behaviorally, or some combination of these (Reisner, Poteat et al., 2016). Health care that is gender-affirming or trans-competent utilizes culturally specific language in caring for TGD people. Gender-affirming care is not synonymous with transition-related care. Provision of transition-related care, such as medical gender affirmation via hormones or surgery, does not alone ensure provision of gender-affirming care, nor does it indicate the quality or safety of the health care provided.

Consultation and partnerships with TGD communities can help to ensure relevancy and inclusivity of the language used in providing health care locally in a particular context and setting.

Statement 1.2

We recommend health care professionals use language in health care settings that upholds the principles of safety, dignity, and respect.

Safety, dignity, and respect are basic human rights (International Commission of Jurists, 2007). We recommend HCPs utilize language and terminology that uphold these human rights when providing care for TGD people. Many TGD people have experienced stigma, discrimination, and mistreatment in health care settings, resulting in suboptimal care and poor health outcomes (Reisner, Poteat et al., 2016; Safer et al., 2016; Winter, Settle et al., 2016). Such experiences include misgendering, being refused care or denied services when sick or injured and having to educate HCPs to be able to receive adequate care (James et al., 2016). Consequently, many TGD people feel unsafe accessing health care. They may avoid health care systems and seek other means of getting health-related needs met, such as taking hormones without a medical prescription or monitoring and relying on peers for medical advice. Furthermore, previous negative experiences in health care settings are associated with future avoidance of care among TGD people.

Many TGD people have been treated unjustly, with prejudice, and without dignity or respect by HCPs, and lack of trust is often a barrier to care. Using language grounded in the principles of safety, dignity, and respect in health care settings is paramount to ensure the health, well-being, and rights of TGD people globally. Language is a significant component of gender-affirming care, but language alone does not resolve or mitigate the systematic abuse and sometimes violence TGD people face globally in care settings. Language is but one important step toward patient/client-centered and equitable health care among TGD people. Other concrete actions HCPs can take include obtaining informed consent and refraining from making assumptions about a person's needs based on their gender or TGD status.

Statement 1.3

We recommend health care professionals discuss with transgender and gender diverse people what language or terminology they prefer.

In providing health care to TGD people, we recommend HCPs discuss with their patients what language or terminology they prefer be used when referring to them. This discussion includes asking TGD people how they would like to be addressed in terms of name and pronouns, how they self-identify their gender, and about the language that should be used to describe their body parts. Utilizing affirming language or terminology is a key component of TGD-affirming care (Lightfoot et al., 2021; Vermeir et al., 2018). Furthermore, these discussions and communications can serve to build rapport and reduce the mistrust many TGD people feel toward HCPs and experience within health care systems. Discussions and usage of language or terminology can also facilitate engagement and retention in care that is not specifically TGD-related, such as uptake of routine preventive screenings and any necessary medical follow-up of findings. In electronic health records, organ/anatomical inventories can be standardly used to inform appropriate clinical care, rather than relying solely on assigned sex at birth and/or gender identity designations.

HCPs and health care settings can implement standardized procedures to facilitate these conversations such as: using intake forms that include chosen pronouns and name, inviting

all staff (regardless of gender, i.e., cisgender, TGD) to use pronouns in introductions, having pronouns accompany names on a document for all patients, and not using gendered honorifics (e.g., Ms., Mr.). Policies for HCPs and health care settings can be put in place to ensure a TGD person's privacy and right to confidentiality, including when they disclose being a TGD person, and if/how to appropriately document. For example, a clinic policy may be to record this information as private and confidential between HCPs and patients/clients, and that it should only be disclosed on a "need to know" basis.

Note

1. A/73/152, Report of the Independent Expert on protection against violence and discrimination based on sexual orientation and gender identity

CHAPTER 2 Global Applicability

People who defy cultural boundaries of sex and gender have existed in cultures worldwide since ancient times, sometimes acknowledged in local language terms (Feinberg, 1996). In contrast to the more recent pathologization of gender diversity as an illness, some cultures traditionally celebrated and welcomed this diversity (e.g., Nanda, 2014; Peletz, 2009). Today, the English language umbrella term transgender and gender diverse (TGD) describes a huge variety of gender identities and expressions, and therefore a population with diverse health care experiences and needs. Together, TGD people represent important aspects of human diversity the World Professional Association for Transgender Health (WPATH) asserts should be valued and celebrated. TGD people continue to make vital contributions to the societies in which they live, although often these are unrecognized.

Disturbingly, many TGD people in the modern world experience stigma, prejudice, discrimination, harassment, abuse and violence, resulting in social, economic and legal marginalization, poor mental and physical health, and even death—a process that has been characterized as a stigma-sickness slope (Winter, Diamond et al., 2016). Experiences such as these (and the anticipation or fear of encountering such experiences) leads to what Meyer has described as minority stress (Meyer, 2003; see also Bockting et al., 2013 writing specifically about TGD people), and are associated with poor physical (e.g. Rich et al, 2020) and psychological (e.g., Bränström et al., 2022; Scandurra et al., 2017; Shipherd et al., 2019, Tan et al., 2021) health outcomes.

Violence against TGD people is a particular problem. Seen from a global perspective, it is widespread, diverse in nature (emotional, sexual and physical, e.g., see Mujugira et al., 2021), and involves a range of perpetrators (including State actors). Statistics on murder, the form of violence most extreme in its consequences, are alarming. Worldwide, there were over 4,000 documented killings between January 2008 and September 2021; a statistic widely regarded as flawed by under-reporting (TGEU, 2020).

Since the publication of the Standards of Care Version 7 (SOC-7), there have been dramatic changes in perspectives on TGD people and their health care. Mainstream global medicine no longer classifies TGD identities as a mental disorder. In the Diagnostic and Statistical Manual Version 5 (DSM-5) from the American Psychiatric Association (APA, 2013), the diagnosis of Gender Dysphoria focuses on any distress and discomfort that accompanies being TGD, rather than on the gender identity itself. A text revision (DSM-5-TR) was published in 2022. In the International Classification of Diseases, Version 11 (ICD-11), the diagnostic manual of the World Health Organization (WHO, 2019b), the Gender Incongruence diagnosis is placed in a chapter on sexual health and focuses on the person's experienced identity and any need for gender-affirming treatment that might stem from that identity. Such developments, involving a depathologization (or more precisely a de-psychopathologization) of transgender identities, are fundamentally important on a number of grounds. In the field of health care, they may have helped support a care model that emphasizes patients' active participation in decision-making about their own health care, supported by primary health care professionals (HCPs) (Baleige et al., 2021). It is reasonable to suppose these developments may also promote more socially inclusive policies such as legislative reform regarding gender recognition that facilitates a rights-based approach, without imposing requirements for diagnosis, hormone therapy and/or surgery. TGD people who have changed gender markers on key documents enjoy better mental health (e.g., Bauer et al., 2015; Scheim et al., 2020). A more rights-based approach in this area may contribute greatly to the overall health and well-being of TGD people (Arístegui et al., 2017).

Previous editions of the SOC have revealed much of the recorded clinical experience and knowledge in this area is derived from North American and Western European sources. They have focused on gender-affirming health care in high income countries that enjoy relatively well-resourced health care systems (including those with trained mental health providers, endocrinologists, surgeons and other specialists) and where services are often funded publicly or (at least for some patients) through private insurance.

For many countries, health care provision for TGD people is aspirational; with resourcing in this area limited or non-existent, and services often unavailable, inappropriate, difficult to access and/ or unaffordable. Few if any HCPs (primary or specialist) may exist. Funding for gender-affirming health care may be absent, with patients often bearing the full costs of whatever health care they access. Health care providers often lack clinical and/or cultural competence in this area. Training for work with these patients may be limited (e.g., Martins et al., 2020). For all these reasons and because of mainstream "Western" medicine's historical view of TGD people as mentally disordered (a perspective that has only recently changed), TGD people have commonly found themselves disempowered as health care consumers.

Health care providers have found the relevant literature is largely North American and European, which present particular challenges for persons working in health care systems that are especially poorly resourced. Recent initiatives that often involve TGD stakeholders as partners are changing this situation somewhat by providing a body of knowledge about good practice in other regions, including how to provide effective, culturally-competent TGD health care in low- and middle-income countries outside the global north.

Within the field, a wide range of valuable health care resources have been developed in recent years. Dahlen et al (2021) review twelve international clinical practice guidelines; over half those reviewed originate from professional bodies based in North America (e.g., Hembree et al., 2017) or Europe (e.g., T'Sjoen et al., 2020). Three are from WHO (the most recent being WHO, 2016). Nowadays, there are numerous other resources, not on Dahlen et al.'s list, that explicitly draw on expertise from regions outside North America and Europe. Examples can be found in Asia and the Pacific (APTN, 2022; Health Policy Project et al., 2015), the Caribbean (PAHO, 2014), Thailand, Australia (Telfer et al., 2020), Aotearoa New Zealand (Oliphant et al., 2018), and South Africa (Tomson et al., 2021) (see also TRANSIT (UNDP et al., 2016)). These resources have commonly been created through the initiatives of or in partnership with TGD communities locally or internationally. This partnership approach,

focused on meeting local needs in culturally safe and competent ways, can also have broad international relevance. Some of these publications may be of particular value to those planning, organizing and delivering services in low-income, low-resource countries. There are likely to be other resources published in languages other than English of which we are unaware.

Globally, TGD identities may be associated with differing conceptual frameworks of sex, gender, and sexuality and exist in widely diverse cultural (and sometimes spiritual) contexts and histories. Considering the complex relationships between social and cultural factors, the law, and the demand for and provisions of gender-affirming health care, the SOC-8 should be interpreted through a lens that is appropriate for and within the context of each HCP's individual practice while maintaining alignment to the core principles that underscore it (APTN and UNDP, 2012; Health Policy Project et al., 2015; PAHO, 2014).

It is within this context and by drawing broadly on the experiences of TGD people and health care providers internationally that we consider the global applicability of SOC-8 within this chapter. We set out key considerations for HCPs and conclude by recommending core principles and practices fundamental to contemporary health care for TGD people, regardless of where they live or whether there are resources available to those who seek to provide such health care.

Statement 2.1
We recommend health care systems should provide medically necessary gender-affirming health care for transgender and gender diverse people.

Medical necessity is a term common to health care coverage and insurance policies globally. A common definition of medical necessity as used by insurers or insurance companies is "Health care services that a physician and/or health care professional, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are: (a) in accordance with generally accepted standards of medical practice; (b) clinically

Statements of Recommendations

2.1- We recommend health care systems should provide medically necessary gender-affirming health care for transgender and gender diverse people.

2.2- We recommend health care professionals and other users of the Standards of Care, Version 8 (SOC-8) apply the recommendations in ways that meet the needs of local transgender and gender diverse communities, by providing culturally sensitive care that recognizes the realities of the countries they are practicing in.

2.3- We recommend health care providers understand the impact of social attitudes, laws, economic circumstances, and health systems on the lived experiences of transgender and gender diverse people worldwide.

2.4- We recommend translations of the SOC focus on cross-cultural, conceptual, and literal equivalence to ensure alignment with the core principles that underpin the SOC-8.

2.5- We recommend health care professionals and policymakers always apply the SOC-8 core principles to their work with transgender and gender diverse people to ensure respect for human rights and access to appropriate and competent health care, including:

General principles
- Be empowering and inclusive. Work to reduce stigma and facilitate access to appropriate health care for all who seek it;
- Respect diversity. Respect all clients and all gender identities. Do not pathologize differences in gender identity or expression;
- Respect universal human rights including the right to bodily and mental integrity, autonomy and self-determination; freedom from discrimination, and the right to the highest attainable standard of health.

Principles around developing and implementing appropriate services and accessible health care
- Involve transgender and gender diverse people in the development and implementation of services;
- Become aware of social, cultural, economic, and legal factors that might impact the health (and health care needs) of transgender and gender diverse people, as well as the willingness and the capacity of the person to access services;
- Provide health care (or refer to knowledgeable colleagues) that affirms gender identities and expressions, including health care that reduces the distress associated with gender dysphoria (if this is present);
- Reject approaches that have the goal or effect of conversion and avoid providing any direct or indirect support for such approaches or services.

Principles around delivering competent services
- Become knowledgeable (get training, where possible) about the health care needs of transgender and gender diverse people, including the benefits and risks of gender-affirming care;
- Match the treatment approach to the specific needs of clients, particularly their goals for gender identity and expression;
- Focus on promoting health and well-being rather than solely the reduction of gender dysphoria, which may or may not be present;
- Commit to harm reduction approaches where appropriate;
- Enable the full and ongoing informed participation of transgender and gender diverse people in decisions about their health and well-being;
- Improve experiences of health services including those related to administrative systems and continuity of care.

Principles around working towards improved health through wider community approaches
- Put people in touch with communities and peer support networks;
- Support and advocate for clients within their families and communities (schools, workplaces, and other settings) where appropriate.

appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient's illness, injury, or disease; and (c) not primarily for the convenience of the patient, physician, or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease." The treating HCP asserts and documents that a proposed treatment is medically necessary for treatment of the condition (American Medical Association, 2016).

Generally, "accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, designated Medical Specialty Societies and/or legitimate Medical Colleges' recommendations, and the views of physicians and/or HCPs practicing in relevant clinical areas.

Medical necessity is central to payment, subsidy, and/or reimbursement for health care in parts of the world. The treating HCP may assert and document that a given treatment is medically necessary for the prevention or treatment of the condition. If health policies and practices challenge the medical necessity of a treatment, there may be an opportunity to appeal to a governmental agency or other entity for an independent medical review.

It should be recognized gender diversity is common to all human beings and is not pathological. However, gender incongruence that causes clinically significant distress and impairment often requires medically necessary clinical

interventions. In many countries, medically necessary gender-affirming care is documented by the treating health professional as treatment for Gender Incongruence (HA60 in ICD-11; WHO, 2019b) and/or as treatment for Gender Dysphoria (F64.0 in DSM-5-TR; APA, 2022).

There is strong evidence demonstrating the benefits in quality of life and well-being of gender-affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people in need of these treatments (e.g., Ainsworth & Spiegel, 2010; Aires et al., 2020; Aldridge et al., 2020; Almazan & Keuroghlian, 2021; Al-Tamimi et al., 2019; Balakrishnan et al., 2020; Baker et al., 2021; Buncamper et al., 2016; Cardoso da Silva et al., 2016; Eftekhar Ardebili, 2020; Javier et al., 2022; Lindqvist et al., 2017; Mullins et al., 2021; Nobili et al., 2018; Owen-Smith et al., 2018; Özkan et al., 2018; T'Sjoen et al., 2019; van de Grift, Elaut et al., 2018; White Hughto & Reisner, Poteat et al., 2016; Wierckx, van Caenegem et al., 2014; Yang, Zhao et al., 2016). Gender-affirming interventions may also include hair removal/transplant procedures, voice therapy/surgery, counseling, and other medical procedures required to effectively affirm an individual's gender identity and reduce gender incongruence and dysphoria. Additionally, legal name and sex or gender change on identity documents can also be beneficial and, in some jurisdictions, are contingent on medical documentation that patients may call on practitioners to produce.

Gender-affirming interventions are based on decades of clinical experience and research; therefore, they are not considered experimental, cosmetic, or for the mere convenience of a patient. They are safe and effective at reducing gender incongruence and gender dysphoria (e.g., Aires et al., 2020; Aldridge et al., 2020; Al-Tamimi et al., 2019; Balakrishnan et al., 2020; Baker et al., 2021; Bertrand et al., 2017; Buncamper et al., 2016; Claes et al., 2018; Eftekhar Ardebili, 2020; Esmonde et al., 2019; Javier et al., 2022; Lindqvist et al., 2017; Lo Russo et al., 2017; Marinkovic & Newfield, 2017; Mullins et al., 2021; Nobili et al., 2018; Olson-Kennedy, Rosenthal et al., 2018; Özkan et al., 2018; Poudrier et al., 2019; T'Sjoen et al., 2019; van de Grift, Elaut et al., 2018; White Hughto & Reisner,

Poteat et al., 2016; Wierckx, van Caenegem et al., 2014; Wolter et al., 2015; Wolter et al., 2018).

Consequently, WPATH urges health care systems to provide these medically necessary treatments and eliminate any exclusions from their policy documents and medical guidelines that preclude coverage for any medically necessary procedures or treatments for the health and well-being of TGD individuals. In other words, governments should ensure health care services for TGD people are established, extended or enhanced (as appropriate) as elements in any Universal Health Care, public health, government-subsidized systems, or government-regulated private systems that may exist. Health care systems should ensure ongoing health care, both routine and specialized, is readily accessible and affordable to all citizens on an equitable basis.

Medically necessary gender-affirming interventions are discussed in SOC-8. These include but are not limited to hysterectomy +/- bilateral salpingo-oophorectomy; bilateral mastectomy, chest reconstruction or feminizing mammoplasty, nipple resizing or placement of breast prostheses; genital reconstruction, for example, phalloplasty and metoidioplasty, scrotoplasty, and penile and testicular prostheses, penectomy, orchiectomy, vaginoplasty, and vulvoplasty; hair removal from the face, body, and genital areas for gender affirmation or as part of a preoperative preparation process; gender-affirming facial surgery and body contouring; voice therapy and/or surgery; as well as puberty blocking medication and gender-affirming hormones; counseling or psychotherapeutic treatment as appropriate for the patient and based on a review of the patient's individual circumstances and needs.

Statement 2.2

We recommend health care professionals and other users of the Standards of Care, Version 8 (SOC-8) apply the recommendations in ways that meet the needs of local transgender and gender diverse communities, by providing culturally sensitive care that recognizes the realities of the countries they are practicing in.

TGD people identify in many different ways worldwide, and those identities exist within a cultural context. In English speaking countries, TGD people variously identify as *transsexual,*

trans, gender nonconforming, gender queer or diverse, nonbinary, or indeed *transgender and/or gender diverse,* as well as by other identities; including (for many identifying inside the gender binary) *male* or *female.* (e.g., James et al., 2016; Strauss et al., 2017; Veale et al., 2019).

Elsewhere, identities include but are not limited to *travesti* (across much of Latin America), *hijra* (across much of South Asia), *khwaja sira* (in Pakistan), *achout* (in Myanmar), *maknyah, paknyah* (in Malaysia), *waria* (Indonesia) *kathoey, phuying kham phet, sao praphet song* (Thailand), *bakla, transpinay, transpinoy* (Philippines), *faʻafafine* (Samoa), *mahu* (French Polynesia, Hawaiʻi), *leiti* (Tonga), *fakafifine* (Niue), *pinapinaaine* (Tuvalu and Kiribati), *vakasalewalewa* (Fiji), *palopa* (Papua Niugini), *brotherboys* and *sistergirls* (Aboriginal and Torres Strait Islander people in Australia), and *akavaʻine* (Cook Islands) (e.g., APTN and UNDP, 2012; Health Policy Project et al., 2015; Kerry, 2014). There are also a large number of *two spirit* identities across North America (e.g., *nadleehi* in Navajo (Diné) culture) (Sheppard & Mayo, 2013). The identities to which each of these terms refer are often culturally complex and may exist in a spiritual or religious context. Depending on the cultures and the identities concerned, some may be regarded as so-called "third genders" lying beyond the gender binary (e.g., Graham, 2010; Nanda, 2014; Peletz, 2009). Some TGD identities are less firmly established than others. In many places worldwide, the visibility of transgender men and nonbinary trans masculine identities is relatively recent, with few or no applicable traditional terms in local languages (Health Policy Project et al., 2015). Regardless of where or with whom HCPs work (including those working with ethnic minority persons, migrants and refugees), they need to be aware of the cultural context in which people have grown up and live as well as the consequences for health care.

Worldwide the availability, accessibility, acceptability and quality of health care vary greatly, with resulting inequities within and across countries (OECD, 2019). In some countries, formal health care systems exist alongside established traditional and folk health care systems, with indigenous models of health underpinning the importance of holistic health care (WHO, 2019a).

HCPs should be aware of the traditions and realities within which health care is available and provide support that is sensitive to the local needs and identities of TGD people and provide them with culturally competent and safe care.

Statement 2.3

We recommend health care providers understand the impact of social attitudes, laws, economic circumstances, and health systems on the lived experiences of transgender and gender diverse people worldwide.

TGD people's lived experiences vary greatly, depending on a range of factors, including social, cultural (including spiritual), legal, economic and geographic. When TGD people live in environments that affirm their gender and/or cultural identities, then these experiences can be very positive. Families are particularly important in this regard (e.g., Pariseau et al., 2019; Yadegarfard et al., 2014; Zhou et al., 2021). However, when viewed from a global perspective, the circumstances in which TGD people live are often challenging. They are commonly denied widely accepted rights in international human rights law. These include rights to education, health and protection from medical abuses, work and an adequate standard of living, housing, freedom of movement and expression, privacy, security, life, family, freedom from arbitrary deprivation of liberty, fair trial, treatment with humanity while in detention, and freedom from torture, inhuman or degrading treatment or punishment (International Commission of Jurists, 2007, 2017).

It is widely accepted that denial of rights can impact sexual and gender minority health and well-being (e.g., OHCHR et al., 2016; WHO, 2015). We therefore reaffirm here the importance of the rights listed above for TGD people and note WPATH's previous rights advocacy, including through numerous policy documents (e.g., WPATH, 2016, 2017, 2019). HCPs can play an important role in rights advocacy, including the right to quality gender-affirming health care that is appropriate, affordable, and accessible.

Across the world, a large number of studies detail the challenges TGD people face in their lives, and the impact on their health and well-being (e.g., Aurat Foundation, 2016;

Bhattacharya & Ghosh, 2020; Chumakov et al., 2021; Coleman et al., 2018; Heylens, Elaut et al., 2014; Human Rights Watch, 2014; James et al, 2016; Lee, Operario et al., 2020; Luz et al., 2022; McNeil et al., 2012, 2013; Motmans et al., 2017; Muller et al., 2019; Scandurra et al., 2017; Strauss et al., 2019; Suen et al., 2017; Valashany & Janghorbani, 2019; Veale et al., 2019; Wu et al., 2017). The research shows TGD people often experience stigma and prejudice as well as discrimination and harassment, abuse and violence, or they live in anticipation and fear of such actions. Social values and attitudes hostile to TGD people, often communicated to young people in school curricula (e.g., Olivier & Thurasukam, 2018), are also expressed in family rejection (e.g., Yadegarfard et al., 2014), and perpetuated in laws, policies and practices that limit freedom to express one's gender identity and sexuality and hinder access to housing, public spaces, education, employment and services (including health care). The end result is TGD people are commonly deprived of a wide range of opportunities available to their cisgender counterparts and are pushed to the margins of society, without family supports. To make matters worse, across much of the world TGD people's access to legal gender recognition is restricted or non-existent (e.g., ILGA World, 2020a; TGEU, 2021; UNDP and APTN, 2017). In some countries, such barriers nowadays draw on support from "gender-critical theorists" (as critiqued by e.g., Madrigal-Borloz, 2021; Zanghellini, 2020).

Gender identity change efforts (gender reparative or gender conversion programs aimed at making the person cisgender) are widespread, cause harm to TGD people (e.g., APTN, 2020a, 2020b, 2020c, 2021; Bishop, 2019; GIRES et al., 2020; Turban, Beckwith et al., 2020), and (like efforts targeting sexual orientation) are considered unethical (e.g., APS, 2021; Trispiotis and Purshouse, 2021; Various, 2019, 2021). These efforts may be viewed as a form of violence. The UN independent expert on protection against violence and discrimination based on sexual orientation and gender identity has called for a global ban on such practices (Madrigal-Borloz, 2020). An increasing number of jurisdictions are outlawing such work (ILGA World, 2020b).

Inequities arise from a range of factors, including economic considerations and values underpinning the provision of health care systems, particularly with regard to the emphasis placed on public-, private- and self-funding of health care. Lack of access to appropriate and affordable health care can lead to a greater reliance on informal knowledge systems. This includes information about self-administration of hormones, which, in many cases, is undertaken without necessary medical monitoring or supervision (e.g., Do et al., 2018; Liu et al., 2020; Rashid et al., 2022; Reisner et al., 2021; Winter & Doussantousse, 2009).

In some parts of the world, large numbers of transgender women employ silicone as a means of modifying their bodies, drawing on the services of silicone "pumpers" and/or attending pumping "parties", often within their communities. The immediate results of silicone pumping contrast with significant downstream health risks (e.g., Aguayo-Romero et al., 2015; Bertin et al., 2019; Regmi et al., 2021), particularly where industrial silicone or other injectable substances have been used and where surgical removal may be difficult.

Finally, sexual health outcomes for TGD people are poor. HIV prevalence for transgender women reporting to clinical organizations in metropolitan areas is approximately 19% worldwide, which is 49 times higher than the background prevalence rate in the general population (Baral et al., 2013). Sexual health outcomes for transgender men are also problematic (e.g., Mujugira et al., 2021).

Statement 2.4

We recommend translations of the SOC focus on cross-cultural, conceptual and literal equivalence to ensure alignment with the core principles that underpin the SOC-8.

Much of the research literature on TGD people is produced in high-income and English-speaking countries. global northern perspectives about TGD people (including those related to health care needs and provision) dominate this literature. A May 2021 Scopus database search undertaken by the current authors shows 99% of the literature on transgender health care comes out of Europe, North America, Australia, or New Zealand. Overall, 96% of the literature is in the English language. TGD people of the Global

South have received relatively little attention in the English language literature, and the work of those HCPs who interact with them has often gone unrecognized and unpublished or has not been translated into English. Applying resources produced in the global north risks overlooking the relevance and nuance of local knowledge, cultural frameworks and practices, and missed opportunities to learn from the work of others.

When translating the principles set out in the SOC, we recommend following best practice guidelines for language translation to ensure high quality written resources are produced that are culturally and linguistically appropriate to the local situation. It is important translators have knowledge about TGD identities and cultures to check that literal translations are culturally competent and safe for local TGD people. It is also important translation should follow established processes for quality assurance (Centers for Medicare & Medicaid Services, 2010; Sprager & Martinez, 2015)

Statement 2.5

We recommend health care professionals and policymakers always apply the SOC-8 core principles to their work with transgender and gender diverse people to ensure respect for human rights and access to appropriate and competent health care, including:

General principles

- Be empowering and inclusive. Work to reduce stigma and facilitate access to appropriate health care, for all who seek it;
- Respect diversity. Respect all clients and all gender identities. Do not pathologize differences in gender identity or expression;
- Respect universal human rights, including the right to bodily and mental integrity, autonomy, and self-determination; freedom from discrimination and the right to the highest attainable standard of health.

Principles around developing and implementing appropriate services and accessible health care

- Involve TGD people in the development and implementation of services;

- Become aware of social, cultural, economic, and legal factors that might impact the health (and health care needs) of transgender and gender diverse people, as well as the willingness and capacity of the person to access services;
- Provide health care (or refer to knowledgeable colleagues) that affirms gender identities and expressions, including health care that reduces the distress associated with gender dysphoria (if this is present);
- Reject approaches that have the goal or effect of conversion, and avoid providing any direct or indirect support for such approaches or services

Principles around delivering competent services

- Become knowledgeable (get training, where possible) about the health care needs of transgender and gender diverse people, including the benefits and risks of gender-affirming care;
- Match the treatment approach to the specific needs of clients, particularly their goals for gender identity and expression;
- Focus on promoting health and well-being rather than solely the reduction of gender dysphoria, which may or may not be present;
- Commit to harm reduction approaches where appropriate;
- Enable the full and ongoing informed participation of transgender and gender diverse people in decisions about their health and well-being;
- Improve experiences of health services, including those associated with administrative systems and continuity of care.

Principles around working towards improved health through wider community approaches

- Put people in touch with communities and peer support networks;
- Support and advocate for clients within their families and communities (schools, workplaces, and other settings) where appropriate.

We have already cited research detailing the broad range of challenges TGD people may face; social economic and legal obstacles, as well those related to health care access. While overall health care services are diverse across the world (in terms of availability, accessibility, and quality), those services available to TGD people are often inadequate. Numerous reports from diverse regions worldwide show, while TGD people may report positive health care experiences, many others do not (e.g., Callander et al., 2019; Costa, da Rosa Filho et al., 2018; Do et al., 2018; Gourab et al., 2019; Health Policy Project et al., 2015; Liu et al., 2020; Motmans et al., 2017; Muller et al., 2019; PAHO, 2014; Reisner et al., 2021; Strauss et al., 2017; TGEU, 2017). Mainstream health care options often do not meet their needs for general, sexual, or gender-affirming health care. Standard patient management procedures at clinics and hospitals often fail to recognize the gender identities of their TGD patients (including where outside of the binary their patients identify). Patients may be housed in wards that are gender inappropriate for them, putting them at risk of sexual harassment. TGD patients often encounter unsupportive or hostile attitudes from HCPs and ancillary staff and may even be refused service. Of great concern, HCPs in some parts of the world are involved in gender identity change efforts of the sort described earlier in this chapter.

Throughout the world, there are many other barriers to the provision of gender-affirming health care. Health care professionals may often be unwilling to provide the services TGD people seek. In some countries, there may be laws or regulations inhibiting or preventing them from doing so. When general practitioners and other health care providers do not have access to clear guidelines in their own language, they may be deterred from providing services. Even in situations where health care is available, patients may

find it is difficult to access because of distance, gatekeeping practices, supply and demand issues that result in long wait lists or cost increases. Indeed, gender-affirming procedures may not be incorporated into a universal health care provision or be covered by private insurance, even though similar procedures may be covered for cisgender patients.

For all these reasons, many TGD people avoid formal health care services whenever they can. Their own communities commonly fill the void, acting as important resources for their members. They provide social and emotional support, often in an otherwise hostile environment. In addition, they often act as reservoirs of shared information about available options for health care, including parallel and informal health care options outside of (and more accessible and affordable than) mainstream medicine. As we saw earlier in this chapter, this often includes sharing of information about silicone and other injectable substances for bodily transformation and about hormones that are self-administered without necessary medical monitoring or supervision. WHO notes TGD individuals who self-administer gender-affirming hormones would benefit from access to evidence-based information, quality products, and sterile injection equipment (WHO, 2021). Access to such information can form part of a broader harm reduction approach (e.g., Idrus & Hyman, 2014).

Putting the important core principles outlined above into practice can improve health care experiences and promote respect for TGD people in all local contexts. This can occur regardless of the realities of a health care system (including the cultural, social, legal, economic context in which health care is provided), the level of provision available, or the TGD people seeking such services.

CHAPTER 3 Population Estimates

In the previous edition of its Standards of Care, Version 7, World Professional Association for Transgender Health (WPATH) identified only a small number of articles attempting to estimate the size of the transgender and gender diverse (TGD) population and characterized the state-of-the-science as "a starting point" requiring further systematic study (Coleman et al., 2012). Since then, the literature on this topic has expanded considerably as evidenced by a number of recent reviews that have sought to synthesize the available evidence (Arcelus et al., 2015; Collin et al., 2016; Goodman et al., 2019; Meier & Labuski, 2013; Zhang et al., 2020).

In reviewing epidemiologic data pertaining to the TGD population, it may be best to avoid the terms "incidence" and "prevalence." Avoiding these and similar terms may preclude inappropriate pathologizing of TGD people (Adams et al., 2017; Bouman et al., 2017). Moreover, the term "incidence" may not be applicable in this situation because it assumes TGD status has an easily identifiable time of onset, a prerequisite for calculating incidence estimates (Celentano & Szklo, 2019). For all the above reasons, we recommend using the terms "number" and "proportion" to signify the absolute and the relative size of the TGD population.

Perhaps the most important consideration in reviewing this literature is the variable definition applied to the TGD population (Collin et al., 2016; Meier & Labuski, 2013). In clinic-based studies, the data on TGD people are typically limited to individuals who received transgender-related diagnoses or counseling or those who requested or underwent gender-affirming therapy, whereas survey-based research typically relies on a broader, more inclusive definition based on self-reported gender identities.

Another methodological consideration in assessing the size and distribution of the TGD population is the need to understand what constitutes the sampling frame. As noted in recent reviews (Goodman et al., 2019; Zhang et al., 2020), many of the published studies, especially those conducted more than a decade ago, first assessed the number of patients seen at a particular clinical center and then divided that number by an approximated population size. This was unlikely to produce an accurate estimate because the numerator in the calculations is not necessarily included in the denominator, and the true size of the denominator often remains unknown.

With these considerations in mind, it is advisable to focus specifically on recent (published within the last decade) peer-reviewed studies that utilized sound methodology in identifying TGD people within a well-defined sampling frame. For all of the above reasons, the present chapter is focused on studies that met the following inclusion criteria 1) appeared in press in 2009 or later; 2) used a clear definition of TGD status; 3) calculated proportions of TGD people based on a well-defined population denominator; and 4) were peer-reviewed. These types of studies can provide more accurate contemporary estimates.

The available studies can be assigned into three groups 1) those that reported proportions of TGD people among individuals enrolled in large health care systems; 2) those that presented results from population surveys of predominantly adult participants; and 3) those that were based on surveys of youth conducted in schools. Of these three categories, the most informative and methodologically sound studies are summarized below. Additional details about these and other similar studies can be found in recent literature reviews (Goodman et al., 2019; Zhang et al., 2020).

Among studies that estimated the size of the TGD population enrolled in large health care systems, all were conducted in the US, and all relied on information obtained from electronic health records. Four of those health system-based studies relied exclusively on diagnostic codes to ascertain the TGD population; two studies (Blosnich et al., 2013; Kauth et al., 2014) used data from the Veterans Health Affairs system, which provides care to over 9 million people, and two studies (Dragon et al., 2017; Ewald et al., 2019) used claims data from Medicare, the federal health insurance program that primarily covers people 65 years of age or older. The proportions of TGD people reported in these diagnostic code-based studies ranged from approximately 0.02% to 0.03%. Another more recent publication also used Medicare data along with commercial insurance claims to identify TGD people and applied expanded inclusion criteria to supplement

diagnostic codes with information on procedures and hormone therapy (Jasuja et al., 2020). Using this methodology, the proportion of TGD people among all persons enrolled in the participating health plans was 0.03%. The sixth health systems-based study (Quinn et al., 2017) was conducted at Kaiser Permanente plans in the states of Georgia and California; these plans provide care to approximately 8 million members enrolled through employers, government programs, or individually. The TGD population in the Kaiser Permanente study was ascertained across all age groups using both diagnostic codes and free-text clinical notes. The proportions of TGD people identified at Kaiser Permanente were higher than the corresponding proportions reported in the Veterans Health Affairs and Medicare studies with the most recent estimates ranging from 0.04 to 0.08%.

In contrast to results from the health system-based studies, findings from surveys that relied on self-reported TGD status produced much higher estimates. Two US studies took advantage of the Behavioral Risk Factor Surveillance Study (BRFSS), which is an annual telephone survey conducted in all 50 states and US territories (Conron et al., 2012; Crissman et al., 2017). The first study used data from the 2007–2009 BRFSS cycles in the state of Massachusetts, and the second study used the 2014 BRFSS data from 19 states and the territory of Guam. Both studies reported that approximately 0.5% of adult participants (at least 18 years of age) responded "Yes" to the question "Do you consider yourself to be transgender?"

An internet-based survey administered to a sample of the Dutch population 15–70 years of age (Kuyper & Wijsen, 2014) asked participants to score the following two questions using a 5-point Likert scale: "Could you indicate to which degree you psychologically experience yourself as a man?" and "Could you indicate to which degree you psychologically experience yourself as a woman?" The respondents were considered "gender ambivalent" if they gave the same score to both statements and "gender incongruent" when they reported a lower score for their sex assigned at birth than for their gender identity. The proportions of participants reporting incongruent

and ambivalent gender identity were 1.1% and 4.6%, respectively, for persons who were assigned male at birth (AMAB), and 0.8% and 3.2%, respectively, for persons assigned female at birth (AFAB).

A similarly designed study estimated the proportion of TGD residents in the Flanders region of Belgium using a sample drawn from the country's National Register (Van Caenegem, Wierckx et al., 2015). Participants were asked to score the following statements: "I feel like a woman" and "I feel like a man" on a 5-point Likert scale. Using the same definitions applied in the Dutch study (Kuyper & Wijsen, 2014), the proportion of gender incongruent individuals was 0.7% for AMAB people and 0.6% for AFAB people. The corresponding estimates for gender ambivalence among AMAB and AFAB people were 2.2% and 1.9%, respectively.

A more recent population-based study evaluated the proportion of TGD people among approximately 50,000 adult residents of Stockholm County, Sweden (Åhs et al., 2018). The numerator was determined by asking participants the following question: "I would like hormones or surgery to be more like someone of a different sex." Two additional items were designed to identify individuals experiencing gender incongruence: "I feel like someone of a different sex" and "I would like to live as or be treated as someone of a different sex." The need for either hormone therapy or gender-affirming surgery was reported by 0.5% of participants. Individuals who expressed feeling like someone of a different sex and those who wanted to live as or be treated as a person of another sex constituted 2.3% and 2.8% of the total sample, respectively.

Population-based data outside of North America and Western Europe are less common. One recent study offers valuable data from a large representative survey of 6,000 adults in Brazil (Spizzirri et al., 2021). Gender identity of participants was assessed based on the following three questions 1) "Which of the following options best describes how you currently feel?" (Options: I feel I am a man, I feel I am a woman, and I feel I am neither a man nor a woman); 2) "What is the sex on your birth certificate?" (Options: male, female, and undetermined); and 3) "Which of

these situations do you most closely relate to?" (Options: I was born male, but I have felt female since childhood; I was born female, but I have felt male since childhood; I was born male, and I feel comfortable with my body; I was born female, and I feel comfortable with my body). Based on the responses to these three questions, the authors determined 1.9% of the survey respondents were TGD (0.7% defined as transgender, and 1.2% defined as nonbinary).

The literature on the population proportions of TGD youth (persons under 19 years of age) includes several survey studies conducted in schools. A 2012 national cross-sectional survey in New Zealand collected information on TGD identity among high school students (Clark et al., 2014). Among over 8,000 survey participants, 1.2% self-identified as TGD and 2.5% reported they were not sure. Another study of schoolchildren was based on a 2016 survey of 9th and 11th grade students (ages 14–18 years) in the US state of Minnesota (Eisenberg et al., 2017). Of the nearly 81,000 survey respondents, 2.7% reported being TGD. A more recent study (Johns et al., 2019) presented results of the Youth Risk Behavior Survey (YRBS), which is conducted biennially among local, state, and nationally representative samples of US high school students in grades 9–12 (approximate age range 13–19 years). The 2017 YRBS cycle was carried out in 10 states and 9 large urban areas and included the following sequence: *"Some people describe themselves as transgender when their sex at birth does not match the way they think or feel about their gender. Are you transgender?"* Among nearly 120,000 participants across the 19 sites, 1.8% responded *"Yes, I am transgender,"* and 1.6% responded *"I am not sure if I am transgender."*

Another recently published school-based study in the US presented results of a 2015 survey conducted in Florida and California with the aim of identifying gender diverse children and adolescents in a sample of just over 6,000 students in grades 9–12 (Lowry et al., 2018). "High gender-nonconforming" was used to define AMAB children who reported being very/mostly/somewhat feminine or AFAB children who reported being very/mostly/somewhat masculine. Based on these definitions, the proportions of

TGD participants were reported to be 13% among AMAB students, 4% among AFAB students, and 8.4% overall.

Only one study examined the proportion of self-identified TGD children in a younger age group. Shields et al. analyzed the data from a 2011 survey of 2,700 students in grades 6–8 (age range 11–13 years) across 22 San Francisco public middle schools (Shields et al., 2013). Thirty-three children self-identified as TGD based on the question *"What is your gender?"* where the possible responses were *"female, male, or transgender."* The resulting proportion of transgender survey respondents was 1.3%. However, this definition would exclude TGD persons self-identifying as nonbinary and those who do not explicitly identify as transgender.

Taken together, these data indicate among health system-based studies that relied on diagnostic codes or other evidence documented in the medical records (Blosnich et al., 2013; Dragon et al., 2017; Ewald et al., 2019; Kauth et al., 2014; Quinn et al., 2017), the proportions of TGD people reported in recent years (2011–2016) ranged from 0.02% to 0.08%. By contrast, when the TGD status was ascertained based on self-report, the corresponding proportions were orders of magnitude higher and reasonably consistent, if the studies used similar definitions. When the surveys specifically inquired about "transgender" identity, the estimates ranged from 0.3% to 0.5% among adults and from 1.2% to 2.7% in children and adolescents. When the definition was expanded to include broader manifestations of gender diversity, such as gender incongruence or gender ambivalence, the corresponding proportions were higher: 0.5% to 4.5% among adults and 2.5% to 8.4% among children and adolescents.

As reviewed elsewhere (Goodman et al., 2019), another noteworthy observation is the continuous increase in both the size and the composition of the TGD population with upward trends in the proportion of TGD people observed in health care systems, through population-based surveys, as well as in the data on legal gender recognition. The higher estimates observed in more recent literature support some of the previous publications indicating the size of TGD population was

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Summary of reported proportions of TGD people in the general population

Health systems-based studies: 0.02–0.1%
Survey-based studies of adults: 0.3–0.5% (transgender), 0.3–4.5% (all TGD)
Survey-based studies of children and adolescents: 1.2–2.7% (transgender), 2.5–8.4% (all TGD)

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likely underestimated in earlier studies (Olyslager & Conway, 2008).

The temporal trends in AMAB to AFAB ratio have also been reported in studies analyzing referrals to clinics as well as data from integrated health systems; this ratio has changed from predominantly AMAB in previous decades to predominantly AFAB in recent years, especially among TGD youth (Aitken et al., 2015; de Graaf, Carmichael et al., 2018; de Graaf, Giovanardi et al. 2018; Steensma et al., 2018; Zhang et al., 2021). The trend towards a greater proportion of TGD people in younger age groups and the age-related differences in the AMAB to AFAB ratio likely represent the "cohort effect," which reflects sociopolitical advances, changes in referral patterns, increased access to health care and to medical information, less pronounced cultural stigma, and other changes that have a differential impact across generations (Ashley 2019d; Pang et al., 2020; Zhang et al., 2020).

Despite recent improvements in the quality of published studies, an important limitation of the existing literature is the relative paucity of peer-reviewed publications from regions outside of Western Europe or North America. Some of the relevant information on global estimates can be obtained from reports supported by the governments or non-governmental organizations (Fisher et al., 2019; Kasianczuk & Trofymenko, 2020), but these reports may be difficult to systematically identify and evaluate until they appear in peer-reviewed literature. Other barriers to evaluating the global distribution of the TGD populations include inadequate access to demographic data and over-representation of English-language journals in the world literature.

These limitations notwithstanding, the available highest-quality data clearly indicate TGD people represent a sizable and growing proportion of the general population. Based on the credible evidence available to date, this proportion may range from a fraction of a percent to several percentage points depending on the inclusion criteria, age group, and geographic location. Accurate estimates of the proportion, distribution, and composition of the TGD population as well as a projection of resources required to adequately support the health needs of TGD people should rely on systematically collected high-quality data, which are now increasingly available. Continuous and routine collection of these data is needed to decrease variability and minimize over- and under-estimation of the reported results. For example, far more accurate and precise estimates should become available when population censuses begin systematically collecting and reporting data on sex assigned at birth and gender identity, including asexual and nonbinary categories, using the now well-validated two-step method. The first such census-based estimate was released by the national statistical office of Canada. Based on the 2021 census data, 100,815 of 30.5 million Canadians self-identified as transgender or nonbinary; this accounted for 0.33% of the population 15 years of age or older (Statistics Canada, 2022). Consistent with the published literature, the proportions of transgender and nonbinary people were much higher for Generation Z (born between 1997 and 2006, 0.79%) and millennials (born between 1981 and 1996, 0.51%) than for Generation X (born between 1966 and 1980, 0.19%), baby boomers (born between 1946 and 1965, 0.15%), and the Interwar and Greatest Generations (born in 1945 or earlier, 0.12%). While these results represent the highest quality data available to date, it is not clear how the population proportions reported in Canada may compare with those in other countries. The variability in the definitions of what constitutes the TGD population and the differences in data collection methods can be reduced further by improving international collaborations.

CHAPTER 4 Education

This chapter will provide a general review of the literature related to education in transgender and gender diverse (TGD) health care. Recommendations are offered at governmental, nongovernmental, institutional, and provider levels with the goal of increasing access to competent, compassionate health care. In turn, this increased access should improve health outcomes in TGD populations. As this is a novel chapter in the World Professional Association for Transgender Health (WPATH) Standards of Care, the intent is to lay the groundwork for the education area and invite a broader and deeper discussion among educators and health professionals.

Health professionals involved in transgender care encompass a broad range of disciplines. Health professional education varies considerably by country or region in terms of structure, licensure, and policy. Published literature on education in TGD health care is predominantly from North America, Europe, Australia and New Zealand. This chapter does not provide a review of the education literature for each discipline, the needs specific to each discipline (which can be found in the relevant chapters), or the needs specific to each country/region's health education system. Greater understanding and research are needed on the intersection of health education systems, licensure, and transgender health across the world.

On a global level, TGD health education is imperative if national and international health disparities are to be addressed. Cultural competency related to TGD communities continues to be lacking. The World Bank Group (2018) reports widespread discrimination, harassment, violence, and abuse affecting TGD people. They also report TGD people face the highest rates of violence and discrimination (World Bank Group, 2018). Although many higher income countries have national antidiscrimination laws with gender identity as a protected characteristic, discrimination in the workplace, in education, and in health care remains problematic (World Bank Group, 2018).

Across disciplines, curricula at all levels—undergraduate, graduate, residency, or continuing education—historically have ignored TGD cultural or clinical education. The Joint Commission (US) has recommended health care organizations "provide educational programs and forums that support the unique needs of the LGBT community" and "offer educational opportunities that address LGBT health issues" (The Joint Commission, 2011). However, this is not enforced.

On an individual level, several questions need answers. What type of education interventions can most effectively address transphobia and lead to long-standing changes in attitudes? What interventions translate into increasing the number of care providers in this area as well as the number of TGD people receiving care? Does clinical exposure increase the confidence of providers over time? What educational interventions lead to improved health outcomes in the TGD population and, if so, when and how did these interventions accomplish this? Although health professions have begun to incorporate TGD health into education using a variety of modalities and at varying levels of training, efforts differ by health profession and are neither systemic nor systematic in nature (e.g., Brennan et al., 2012; Chinn, 2013; Eliason et al., 2010; Lim et al., 2015; Obedin-Maliver et al., 2011; Rondahl, 2009).

Attaining cultural humility with the full appreciation of the intersectionality of humanity is an ultimate educational goal. That said, this initial call for education is focused on building the foundation in cultural awareness and cultural competency that is currently weak or non-existent in much of the world.

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statements of Recommendations

4.1- We recommend all personnel working in governmental, nongovernmental, and private agencies receive cultural-awareness training focused on treating transgender and gender diverse individuals with dignity and respect.

4.2- We recommend all members of the health care workforce receive cultural-awareness training focused on treating transgender and gender diverse individuals with dignity during orientation and as part of annual or continuing education.

4.3- We recommend institutions involved in the training of health professionals develop competencies and learning objectives for transgender and gender diverse health within each of the competency areas for their specialty.

Recommendation 4.1

We recommend all personnel working in governmental, nongovernmental, and private agencies receive cultural-knowledge training focused on treating transgender and gender diverse individuals with dignity and respect.

Article 1 of the United Nations Universal Declaration of Human Rights states, "All human beings are born free and equal in dignity and rights" (United Nations, 1948). Only recently has this fundamental statement included the recognition that TGD rights are human rights (UNOCHR, 2018). Globally, training at all levels about TGD communities continues to be lacking. As recently as 2002, only 3% of Fortune 500 companies had antidiscrimination protection for TGD employees, and none offered insurance coverage for gender-affirming health care (Human Rights Campaign Foundation, 2017). By 2022, 91% of Fortune 500 companies included gender identity in US non-discrimination policies, and 66% offered TGD-inclusive insurance coverage. However, only 72% provide any form of lesbian, gay, bisexual, transgender and queer/questioning (LGBTQ) cultural knowledge training for their workforce (Human Rights Campaign Foundation, 2022). This lack of understanding fosters discrimination across the board. Taken together, these inconsistencies negatively affect the health of individuals and communities and exacerbate the health disparities and inequities they face. In Britain, only 28% of TGD workers felt the senior leadership were committed to TGD equality; only 21% of TGD employees would consider reporting transphobic harassment in the workplace (Stonewall, 2018). For those who are openly TGD, 34% were excluded by their co-workers, 35% were abused by customers, 24% were denied promotion due to their gender identity, and 11% were fired (Stonewall, 2018). In southeastern Europe, the World Bank stated there is widespread discrimination, harassment, violence, and abuse, and TGD people in that region faced the highest rates of violence and discrimination (World Bank Group, 2018). Often the discrimination went unreported with 60% of individuals not filing a report because of a lack of faith the complaint would be addressed, a fear of further discrimination or ridicule, and a reluctance to be outed (World Bank Group, 2018). Although many countries in the region have national antidiscrimination laws with gender identity as a protected characteristic, discrimination in the workplace, in education, and in health care remains problematic (World Bank Group, 2018). It is the responsibility of the governmental, nongovernmental, and private agencies in these countries with anti-discrimination laws to ensure the rights of the TGD population. They are, therefore, obligated to find ways in which discrimination and stigma can be decreased. One of these is through education. Local cultures that foster anti-TGD attitudes are often a barrier to this needed education. Although cultural competency trainings have led to equivocal results, Shepherd (2019) recommends that providing cultural knowledge training that prioritizes local cultural issues and focuses on the values of openness, non-judgment, and responsiveness may lead to the desired results. Implementing cultural knowledge training requires a leadership willing to prioritize the training and to dedicate the time, money, and human capital to delivering initial and ongoing training.

Recommendation 4.2

We recommend all members of the health care workforce receive cultural-knowledge training focused on treating transgender and gender diverse individuals with dignity during orientation and as part of annual or continuing education.

Across disciplines, curricula at all levels—undergraduate, graduate, residency, or continuing

education—historically have ignored TGD cultural or clinical education. Factors contributing to this lack of inclusion include lack of faculty knowledge, experience, comfort with the subject matter, faculty bias, limited space within the existing curriculum, and lack of guidance on how to integrate the topics (McDowell & Bower, 2016). Research into the lack of and the need for such education does not specifically address TGD health concerns. Rather, the existing literature subsumes TGD health education within the broader discussion of the lack of LGBTQ-focused cultural and clinical-competency training. As an example, nursing baccalaureate programs included only an average of 2.12 hours of instruction on LGBTQ health (Lim et al., 2015). A fair assumption is that the amount of time devoted to TGD-specific health issues constituted only a fraction of this time.

Within the broader context of LGBTQ competency, the lack of TGD cultural- and clinical-competency training is a long-known shortfall of health care education (Aldridge et al., 2021). In the US, the Department of Health and Human Services' *Healthy People 2020*, (United States Department of Health and Human Services (2013, April 10)), the National Academy of Medicine (The Institute of Medicine, 2011), and the Joint Commission (The Joint Commission, 2011) all recognized lack of education negatively impacts the ability of LGBTQ people, including TGD individuals, to obtain appropriate, medically necessary care. The UK's House of Commons Women and Equalities Committee found lack of education contributed to TGD health disparities in the National Health Service (House of Commons Women and Equalities Committee, 2015, December 8). The lack of TGD health care education has been identified in the US (Obedin-Maliver et al., 2011), UK (Tollemache et al., 2021), South Africa (de Vries et al., 2020; Taylor et al., 2018; Wilson et al., 2014), Canada (Bauer et al., 2014), Australia (Riggs & Bartholomaeus, 2016), Sweden, Spain, Serbia, Poland (Burgwal et al., 2021), and Pakistan (Martins et al., 2020) among other countries.

In addition to developing curriculum, Shepherd (2022) states both clinical and organizational components are necessary to improve clinical encounters and consumer satisfaction. On an organizational level, it must be feasible as well as locally and practically oriented (Shepherd, 2022). On an individual level, in addition to knowledge training, health care professionals are better served employing generic traits that focus on the values of openness, non-judgment, and responsiveness (Shepherd, 2018).

Recommendation 4.3.
We recommend institutions involved in the training of health professionals develop competencies and learning objectives for transgender and gender diverse health within each of the competency areas for their specialty.

Each health profession has its own educational institutions, administrative, and licensing bodies, which vary by country and specialization within the profession. No major health professional organizations, educational institutions, or licensing bodies appear to require training in TGD health. While these organizations increasingly recommend including LGBTQ intersex health, rarely do they specify competencies, skills, or learning objectives for working with TGD people within their specialty. Published material on health professional education in TGD health is focused primarily on nursing, medicine, and mental health and is predominantly from North America, Europe, Australia, and New Zealand. An increased understanding of transgender health and medical/health professional education systems and requirements globally is essential.

Despite the increasing visibility of TGD people, access to knowledgeable and culturally- competent health professionals remain an overwhelming need around the world (James et al., 2016; Lerner et al., 2020; Müller, 2017). Lack of knowledgeable providers is a major barrier to gender-affirming care for transgender persons (Puckett et al., 2018; Safer et al., 2016) and contributes to large health disparities (Giffort & Underman, 2016; Reisman et al., 2019). The lack of adequate professional education in TGD health is a global problem (Do & Nguyen, 2020; Martins et al., 2020; Parameshwaran et al., 2017) that occurs at all levels of training (Dubin et al., 2018) and traverses health disciplines (Glick et al., 2020; Gunjawate et al., 2020; Johnson & Federman,

2014) and medical specialties (Fung et al., 2020; Korpaisarn and Safer, 2018).

Challenges remain as studies to date have small sample sizes, involve one-time training, include multiple disciplines at multiple career levels, focus on short-term outcomes, and often cover all LGBTQI topics rather than TGD-specific ones that are usually acquired post-licensure and are not the focus of most currently studied educational interventions (Dubin et al., 2018).

To successfully implement the recommendations, institutions may need to consider developing 1) systemic and systematic approaches to developing and implementing competencies for each health discipline across the professional lifespan; 2) standardized assessments for learners, with input from the TGD community; and 3) allotment of curricular resources, including trained faculty, as well as time in accordance with clear, consensual learning objectives (Dubin et al., 2018; Pratt-Chapman, 2020). In addition, evaluations of these interventions should not only focus on outcomes but also strive to understand how, when, and why these outcomes are occurring (Allen et al., 2021).

CHAPTER 5 Assessment of Adults

This chapter provides guidance for the assessment of transgender and gender diverse (TGD) adults who are requesting medically necessary gender-affirming medical and/or surgical treatments (GAMSTs) to better align their body with their gender identity (see medically necessary statement in Chapter 2—Global Applicability, Statement 2.1).

TGD adults are people at or above the age of majority in their country, who have some form of gender diversity. The developmental elements of the adolescent chapter, including the importance of parental/caregiver involvement, may be relevant for the care of young adults too, even if they are above the age of majority.

This chapter includes all forms of gender identities and transitions including, but not limited to, male, female, gender diverse, nonbinary, agender, and eunuch. The population of TGD adults is heterogeneous and will vary according to their clinical need, biological, psychological, and social situations, as well as their access to health care. As such, any assessment for GAMSTs will need to be adapted to the scientific, clinical, and community knowledge base of the presenting gender identity as well as local circumstances. This chapter recognizes individuals may experience different local levels of clinical or regulatory oversight when the state or others are providing health care.

An individual's gender identity is an internal identification and experience. The role of the assessor is to assess for the presence of gender incongruence and identify any co-existing mental health concerns, to offer information about GAMSTs, to support the TGD person in considering the effects/risks of GAMSTs, and to assess if the TGD person has the capacity to understand the treatment being offered and if the treatment is likely to be of benefit. The assessor can also assist a TGD person to consider choices that could improve their GAMST outcomes. The GAMST assessment approach described in this chapter recognizes the lived experience and self-knowledge of the TGD person and the clinical knowledge of the assessing health care professional (HCP). Consequently, with this approach, the decision to move forward with GAMSTs is shared between the TGD person and the assessing HCP, with both playing a key part in collaborative decision-making.

Some systems use a model of care for TGD adults seeking GAMSTs that prioritizes the TGD adult as the decision maker with the HCP acting as an advisor, barring serious contraindications. These models are used when considering hormone therapy rather than surgery and are often called "informed consent" models (Deutsch, 2011, 2016a). Many such models utilize an abbreviated assessment that focuses primarily on the ability of a TGD person to grant informed consent and to utilize information about GAMSTs to inform their medical decision-making. There is significant variability in such models across jurisdictions, systems, and HCPs (Deutsch, 2011; Morenz et al., 2020). Informed consent models have been used for some time for hormone prescription in many local settings.

This chapter is intended to offer flexible global guidance that must be adapted to local circumstances. HCPs will need to determine which assessment approaches best meet the needs in their local settings. The evaluation of these approaches is best undertaken in collaboration with TGD people.

Since TGD people represent a diverse array of gender identities and expressions and have differing needs for GAMSTs, no single assessment process will fit every person or every situation. Some TGD people may need a comparatively brief assessment process for GAMSTs. For TGD adults with a complex presentation or for those who are requesting less common treatments or treatments with limited research evidence, more comprehensive assessments with different members of a multidisciplinary team will be required. Assessments may be in person or through telehealth. While psychometric assessment tools have been used in some instances, they are not a required part of the assessment for GAMSTs. Counseling or psychotherapy can be helpful when requested by a TGD person. However, counseling or psychotherapy specifically focused on their TGD identity is not a requirement for the assessment or initiation of GAMSTs. Genital exams are not a prerequisite for initiation of GAMTs and should be performed only when clinically indicated.

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GAMSTs can be delivered in diverse settings. Settings will depend on available health care systems within each country and may include nationalized/public health care, private sector settings, community health care settings, and charitable institutions. Local and regional circumstances may therefore influence the availability of health care. Regardless of the setting, health care offered to TGD people should be of the highest possible quality. World Professional Organization for Transgender Health (WPATH) advocates for assessment and treatment to be readily available. Access to assessment and treatment for TGD people seeking GAMSTs is critical given the clear medical necessity of these interventions and the profound benefits they offer to TGD people (Aldridge et al., 2020; Byne et al., 2012). The guidance in this chapter will need to be adapted according to local, as well as individual, clinical, and social circumstances.

The statements below are based on significant background literature, including literature demonstrating the strong positive impact of access to GAMSTs; available empirical evidence; a favorable risk-benefit ratio; and consensus of professional best practice. The empirical evidence base for the

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Statements of Recommendations

5.1- We recommend health care professionals assessing transgender and gender diverse adults for physical treatments:

5.1.a- Are licensed by their statutory body and hold, at a minimum, a master's degree or equivalent training in a clinical field relevant to this role and granted by a nationally accredited statutory institution.

5.1.b- For countries requiring a diagnosis for access to care, the health care professional should be competent using the latest edition of the World Health Organization's International Classification of Diseases (ICD) for diagnosis. In countries that have not implemented the latest ICD, other taxonomies may be used; efforts should be undertaken to utilize the latest ICD as soon as practicable.

5.1.c- Are able to identify co-existing mental health or other psychosocial concerns and distinguish these from gender dysphoria, incongruence, and diversity.

5.1.d- Are able to assess capacity to consent for treatment.

5.1.e- Have experience or be qualified to assess clinical aspects of gender dysphoria, incongruence, and diversity.

5.1.f- Undergo continuing education in health care relating to gender dysphoria, incongruence, and diversity.

5.2- We suggest health care professionals assessing transgender and gender diverse adults seeking gender-affirming treatment liaise with professionals from different disciplines within the field of transgender health for consultation and referral, if required.

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (all should be met):

5.3- We recommend health care professionals assessing transgender and gender diverse adults for gender-affirming medical and surgical treatment:

5.3.a- Only recommend gender-affirming medical treatment requested by a TGD person when the experience of gender incongruence is marked and sustained.

5.3.b- Ensure fulfillment of diagnostic criteria prior to initiating gender-affirming treatments in regions where a diagnosis is necessary to access health care.

5.3.c- Identify and exclude other possible causes of apparent gender incongruence prior to the initiation of gender-affirming treatments.

5.3.d- Ensure that any mental health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.

5.3.e- Ensure any physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.

5.3.f- Assess the capacity to consent for the specific physical treatment prior to the initiation of this treatment.

5.3.g- Assess the capacity of the gender diverse and transgender adult to understand the effect of gender-affirming treatment on reproduction and explore reproductive options with the individual prior to the initiation of gender-affirming treatment.

5.4- We suggest, as part of the assessment for gender-affirming hormonal or surgical treatment, professionals who have competencies in the assessment of transgender and gender diverse people wishing gender-related medical treatment consider the role of social transition together with the individual.

5.5- We recommend transgender and gender diverse adults who fulfill the criteria for gender-affirming medical and surgical treatment require a single opinion for the initiation of this treatment from a professional who has competencies in the assessment of transgender and gender diverse people wishing gender-related medical and surgical treatment.

5.6- We suggest health care professionals assessing transgender and gender diverse people seeking gonadectomy consider a minimum of 6 months of hormone therapy as appropriate to the TGD person's gender goals before the TGD person undergoes irreversible surgical intervention (unless hormones are not clinically indicated for the individual).

5.7- We recommend health care professionals assessing adults who wish to detransition and seek gender-related hormone intervention, surgical intervention, or both, utilize a comprehensive multidisciplinary assessment that will include additional viewpoints from experienced health care professional in transgender health and that considers, together with the individual, the role of social transition as part of the assessment process.

assessment of TGD adults is limited. It primarily includes an assessment approach that uses specific criteria that are examined by an HCP in close cooperation with a TGD adult and does not include randomized controlled trials or long-term longitudinal research (Olsen-Kennedy et al., 2016). This is understandable given the complexity and ethical considerations of allocating patients in need of care to different assessment groups and the lack of funding for research and other resources to assess long-term outcomes of assessment approaches.

The creation of this guidance has been a complex undertaking. The criteria in this chapter have been significantly revised from SOC-7 to reduce requirements and unnecessary barriers to care. It is hoped that future research will explore the effectiveness of this model as well as evolving assessment models for hormone therapy and for surgery that will allow continued improvements to be made.

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 5.1.

We recommend health care professional assessing transgender and gender diverse adults for gender-affirming treatments:

Statement 5.1.a

Are licensed by their statutory body and hold, at a minimum, a master's degree or equivalent training in a clinical field relevant to this role and granted by a nationally accredited statutory institution.

TGD people, as with all other people seeking health care, should have the highest quality of care accessible that is commensurate with the quality of care provided to all people utilizing health services (The Yogyakarta Principles, 2017). As this will vary around the globe, the nature of the professional completing an assessment for GAMSTs will vary according to the nature of health care in the local setting as well as the regulatory requirements set by licensing and registration boards. It

is important the health care provided includes an assessment conducted by a competent, statutorily regulated HCP who has the competence to identify gender incongruence and conditions that can be mistaken for gender incongruence and who can support the TGD person throughout the assessment process (RCGP, 2019). Assessors must be able to refer to HCPs licensed to provide GAMSTs.

HCPs should have at a minimum a masters-level qualification in a clinical field related to transgender health or equivalent further clinical training and be statutorily regulated; examples include a mental health professional (MHP), general medical practitioner, nurse, or other qualified HCP. In some settings, statutorily regulated HCPs with lower levels of qualification may practice under the clinical supervision of a qualified HCP who takes ultimate clinical responsibility for the quality and accuracy of the completed GAMST assessment. For additional information see Chapter 4—Education.

Accessing a competent, statutorily regulated, HCP with expertise in GAMST assessment can sometimes be difficult. Consequently, ensuring continuity of care and minimizing gaps in accessible care or significantly delayed care (e.g., a long waiting list) may require that a statutorily regulated HCP without expertise provide care and support the assessment of a TGD person for GAMSTs. Avoiding unnecessary delays in care is critically important. However, TGD people should be supported to access care with an experienced HCP as soon as possible (RCGP, 2019).

Established practice requires the competence to identify and diagnose gender incongruence (Hembree et al., 2017; Reed et al., 2016; T'Sjoen et al., 2020) and the ability to identify differentials or conditions that may be mistaken as gender incongruence (Byne et al., 2018; Dhejne et al., 2016; Hembree et al., 2017). Established practice also strongly emphasizes the need for ongoing continuing education in the assessment and provision of care of TGD people (American Psychological Association, 2015; T'Sjoen et al., 2020). For more information see Chapter 4—Education.

Statement 5.1.b

For countries requiring a diagnosis for access to care, the health care professional should be competent using the latest edition of the World Health

Organization's International Classification of Diseases (ICD) for diagnosis. In countries that have not implemented the latest ICD, other taxonomies may be used; efforts should be undertaken to utilize the latest ICD as soon as practicable.

In some countries, a diagnosis of gender incongruence may be necessary to access GAMSTs (as described below). HCPs assessing TGD people in those countries should be competent to diagnose gender incongruence using the most current classification system necessary for TGD people to access GAMSTs. The ICD-11 (WHO, 2019a) is a classification system that focuses on the TGD person's experienced identity and any need for GAMSTs and does not consider a TGD identity to be a mental illness.

Statement 5.1.c
Are able to identify co-existing mental health or other psychosocial concerns and distinguish these from gender dysphoria, incongruence, and diversity.

Gender diversity is a natural variation in people and is not inherently pathological (American Psychological Association, 2015). However, assessment is best provided by an HCP who possesses some expertise in mental health in order to identify conditions that can be mistaken for gender incongruence. Such conditions are rare and, when present, are often psychological in nature (Byne et al., 2012; Byne et al., 2018; Hembree et al., 2017).

The need to include an HCP with some expertise in mental health does not require the inclusion of a psychologist, psychiatrist, or social worker in each assessment. Instead, a general medical practitioner, nurse, or other qualified HCP could also fulfill this requirement if they have sufficient expertise to identify gender incongruence, recognize mental health concerns, distinguish between these concerns and gender dysphoria, incongruence, and diversity, assist a TGD person in care planning and preparation for GAMSTs, and refer to a mental health professional (MHP), if needed. As discussed in greater depth in the mental health chapter, MHPs have an important role to play in the care of TGD people. For example, the prejudice and discrimination experienced by some TGD people (Robles et al., 2016) can lead to depression, anxiety, or worsening of other mental health conditions. In such cases, an MHP can diagnose, clarify, and treat mental health conditions. MHPs and HCPs with expertise in mental health are well-placed to assess for GAMSTs, as well as to support TGD people who require or request mental health input or support during their transition. For additional information see Chapter 18—Mental Health.

Statement 5.1.d
Are able to assess capacity to consent for treatment.

An assessment for GAMSTs must include an examination of the TGD person's ability to consent to the proposed treatment. Consent requires the cognitive capacity to understand the risks and benefits of a treatment and the potential negative and positive outcomes. It also requires the ability to retain that information for the purposes of making the decision (using aids as necessary) as well as the cognitive ability to use that understanding to make an informed decision (American Medical Association, 2021; Applebaum, 2007).

Some TGD individuals will have the capacity to grant consent immediately during the assessment. Some TGD individuals may need a longer process to be able to consent through ongoing discussion and the practice of medical decision-making skills. The presence of psychiatric illness or mental health symptoms do not pose a barrier to GAMSTs unless the psychiatric illness or mental health symptoms affect the TGD person's capacity to consent to the specific treatment being requested or affect their ability to receive treatment. This is especially important because GAMSTs have been found to reduce mental health symptomatology for TGD people (Aldridge et al., 2020).

Health care systems can consider GAMSTs for individuals who may not be able to directly consent if an appropriate legal guardian or regulator-approved independent decision maker with the power to determine health care treatment grants consent and confirms the proposed treatment is in alignment with the TGD individual's needs and wishes.

Statement 5.1.e
Have experience or be qualified to assess clinical aspects of gender dysphoria, incongruence, and diversity. For supporting text, see Statement 5.1.f.

Statement 5.1.f

Undergo continuing education in health care relating to gender dysphoria, incongruence, and diversity.

As in any other area of clinical practice, it is vital HCPs who are providing assessment for the initiation of GAMSTs are knowledgeable and experienced in the health care of TGD people. If this is not possible in the local context, the HCP providing the assessment should work closely with an HCP who is knowledgeable and experienced. As part of their clinical practice, HCPs should commit to ongoing training in TGD health care, become a member of relevant professional bodies, attend relevant professional meetings, workshops or seminars, consult with an HCP with relevant experience, and/or engage with the TGD community. This is particularly important in TGD health care as it is a relatively new field, and the knowledge and terminology are constantly changing (American Psychological Association, 2015; Thorne, Yip et al., 2019). Consequently, keeping up to date in the areas of TGD health is vital for anyone involved in an assessment for GAMSTs.

Statement 5.2

We suggest health care professionals assessing transgender and gender diverse adults seeking gender-affirming treatment liaise with professionals from different disciplines within the field of transgender health for consultation and referral, if required.

If required and if possible, assessment for GAMST should be conducted by a multidisciplinary team (Costa, Rosa-e-Silva et al., 2018; Hembree et al., 2017; Karasic & Fraser, 2018; T'Sjoen et al., 2020) with team members who have timely and adequate contact with one another. This could include an MHP, an endocrinologist, a primary care provider, a surgeon, a voice and communication specialist, TGD peer navigator, and others. In some cases, a multidisciplinary team may not be required; however, should a multidisciplinary team be needed, it is critical HCPs be able to access colleagues from different disciplines in a timely manner to complete the GAMST assessment and best support the needs of the TGD person. It is also critical TGD people be supported with follow-up appointments with any HCP who was involved during the assessment for GAMSTs, prior to,

during, and after the initiation of gender-affirming treatments.

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (all should be met):

Statement 5.3

We recommend health care professionals assessing transgender and gender diverse adults for gender-affirming medical and surgical treatment:

Statement 5.3.a

Only recommend gender-affirming medical treatment requested by a TGD person when the experience of gender incongruence is marked and sustained.

To access GAMSTs, a TGD person's gender incongruence must be marked and sustained. This can include a need for GAMSTs and a desire to be accepted as a person of the experienced gender. Consequently, a consideration of the nature, length and consistency of gender incongruence is important. This can include such factors as a change of name and identity documents, telling others about one's gender, health care documentation, or changes in gender expression. However, marked and sustained gender incongruence can exist in the absence of disclosure to others by the TGD person (Brumbaugh-Johnson & Hull, 2019; Saeed et al., 2018; Sequeira et al., 2020). An abrupt or superficial change in gender identity or lack of persistence is insufficient to initiate gender-affirming treatments, and further assessment is recommended. In such circumstances, ongoing assessment is helpful to ensure the consistency and persistence of gender incongruence before GAMSTs are initiated.

While marked and sustained gender incongruence should be present, it is not necessary for TGD people to experience severe levels of distress regarding their gender identity to access gender-affirming treatments. In fact, access to gender-affirming treatment can act as a prophylactic measure to prevent distress (Becker et al., 2018; Giovanardi et al., 2021; Nieder et al., 2021; Nobili et al., 2018; Robles et al., 2016). A TGD adult can have sustained gender incongruence without significant distress and still benefit from GAMSTs.

Established clinical practice examines the persistence of gender incongruence when considering the initiation of GAMSTs (Chen & Loshak, 2020). In a review of 200 clinical notes, Jones, Brewin et al. (2017) identified the importance of the "stability of gender identity" when planning care. Providing GAMSTs to TGD people with persistent gender incongruence has been associated with low rates of patient regret and high rates of patient satisfaction (Becker et al., 2018; El-Hadi et al., 2018; Staples et al., 2020; Wiepjes et al., 2018). However, while the ICD 11 (WHO, 2019a) requires the presence of marked and persistent gender incongruence for a diagnosis of gender incongruence to be made, there is little specific evidence concerning the length of persistence required for treatment in adults. HCPs involved in an assessment of a TGD person for GAMSTs are encouraged to give due consideration to the life stage, history, and current circumstances of the adult being assessed.

Statement 5.3.b

Ensure fulfillment of diagnostic criteria prior to initiating gender-affirming treatments in regions where a diagnosis is necessary to access health care.

A diagnosis of gender incongruence may be necessary in some regions to access transition-related care. When a diagnosis is necessary to access GAMSTs, the assessment for GAMSTs will involve determining and assigning a diagnosis. In these instances, HCPs should have competence using the latest International Classification of Diseases and Related Health Problems (ICD) (WHO, 2019a). In regions where a diagnosis is necessary to access health care, a diagnosis of HA60 *Gender Incongruence of Adolescence or Adulthood* should be determined prior to gender-affirming interventions. Gender-affirming interventions secondary to a diagnosis of *HA6Z Gender Incongruence, Unspecified* may be considered in the context of a more comprehensive assessment by the multidisciplinary team.

There is evidence the use of rigid assessment tools for "transition readiness" may reduce access to care and are not always in the best interest of the TGD person (MacKinnon et al., 2020). Therefore, in situations where the assignment of a diagnosis is mandatory to access care, the process should be approached with trust and transparency between the HCP and the TGD individual requesting GAMST, with the needs of the TGD individual in mind. Indeed, high quality relationships between TGD people and their HCPs are associated with lower emotional distress and better outcomes (Kattari et al., 2016). Because many TGD people fear HCPs will erroneously conflate transgender identity with mental illness (Ellis et al., 2015), a diagnostic assessment should be undertaken with sensitivity to facilitate the best relationship between the provider and the TGD individual.

Statement 5.3.c

Identify and exclude other possible causes of apparent gender incongruence prior to the initiation of gender-affirming treatments.

In rare cases, TGD individuals might have a condition that may be mistaken for gender incongruence or may have another reason for seeking treatment aside from the alleviation of gender incongruence. In these cases, and when there is ambiguity regarding the diagnosis of gender incongruence, a more detailed and comprehensive assessment is important. For example, further assessment might be required to determine if gender incongruence persists outside of an acute psychotic episode. If gender incongruence persists after an acute psychotic episode resolves, GAMSTs may be considered as long as the TGD person has the capacity to consent to and undergo the specific treatment. If gender incongruence does not persist and only occurs during such an episode, treatment should not be considered. It is important such circumstances be identified and excluded prior to the initiation of GAMSTs (Byne et al., 2012, 2018; Hembree et al., 2017). It is important to understand, however, TGD people may present with gender incongruence and with a mental health condition, autistic spectrum disorder, or other neurodiversity (Glidden et al., 2016). Indeed, some mental health conditions, such as anxiety (Bouman et al., 2017), depression (Heylens, Elaut et al., 2014; Witcomb et al., 2018), and self-harm (Arcelus et al., 2016; Claes et al., 2015) are more prevalent in TGD people who have not accessed GAMSTs. Recent longitudinal studies suggest mental health symptoms experienced by TGD people tend to improve following GAMSTs (Aldridge et al., 2020; Heylens, Verroken et al., 2014;

White Hughto & Reisner, 2016). There is no evidence to suggest a benefit of withholding GAMSTs from TGD people who have gender incongruence simply on the basis that they have a mental health or neurodevelopmental condition. For more information see Chapter 18—Mental Health.

Statement 5.3.d

Ensure any mental health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.

Like their cisgender counterparts, TGD people may have mental health problems. Treatment for mental health problems can and should occur in conjunction with GAMSTs when medical transition is needed. It is vital gender-affirming care is not impeded unless, in some extremely rare cases, there is robust evidence that doing so is necessary to prevent significant decompensation with a risk of harm to self or others. In those cases, it is also important to consider the risks delaying GAMSTs poses to a TGD person's mental and physical health (Byne et al., 2018).

In general, social and medical transition of TDG people are both associated with a reduction in mental health problems (Aldridge et al., 2020; Bouman et al., 2017; Durwood et al., 2017; Glynn et al., 2016; Hughto & Reisner, 2016; Wilson et al., 2015; Witcomb et al., 2018). Unfortunately, the loss of social support and the physical and financial stress that can be associated with the initiation of GAMSTs may exacerbate pre-existing mental health problems and warrant additional support from the treating HCP (Budge et al., 2013; Yang, Wang et al., 2016). An assessment of mental health symptoms can improve transition outcomes, particularly when the assessment is used to facilitate access to psychological and social support during transition (Byne et al., 2012). A delay of transition in rare circumstances may be considered if, for example, the TGD person is unable to engage with the process of transition or would be unable to manage aftercare following surgery, even with support. Where a delay in GAMST as a last resort has been found to be necessary,

the HCP should offer resources and support to improve mental health and facilitate re-engagement with the GAMST process as soon as practicable. It should be noted access to medical transition for TGD people facilitates social transition and improves safety in public (Rood et al., 2017). In turn, the degree to which TGD people's appearance conforms to their gender identity is the best predictor of quality of life and mental health outcomes following medical transition (Austin & Goodman, 2017). Delaying access to GAMSTs due to the presence of mental health problems may exacerbate symptoms (Owen-Smith et al., 2018) and damage rapport; consequently, this should be done only when all other avenues have been exhausted.

Statement 5.3.e

Ensure any physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.

In rare cases, GAMSTs, such as hormonal and surgical interventions, may have iatrogenic consequences or may exacerbate pre-existing physical health conditions (Hembree et al., 2017). In these instances, care should be taken, whenever possible, to manage pre-existing physical health conditions while initiating (if appropriate) or continuing gender-affirming treatments. Any interruptions in treatment should be as brief as possible and with treatment re-initiated as soon as practicable. Limited data and inconsistent findings suggest an association between cardiovascular and metabolic risks and hormone therapy in TGD adults (Getahun, 2018; Iwamoto, Defreyne et al., 2019; Iwamoto et al., 2021; Spanos et al., 2020). Because of the possible harm related to long-term treatment and the probable benefits expected from the preventive measures applied before and during hormone treatment, a careful assessment of physical health conditions prior to initiation of treatment is important. Some specific conditions, such as a history of hormone-sensitive cancer, may require further assessment and management that may preclude hormone treatment (Center of Excellence for Transgender Health, 2016; Hembree et al., 2017).

Similar concerns may be present for TGD adults who wish to access surgical interventions. Each gender-affirming surgical intervention has specific risks and potentially unfavorable consequences (Bryson & Honig, 2019; Nassiri et al., 2020; Remington et al., 2018). However, intervention-specific risks associated with the presence of specific physical conditions have not been well researched. Thus, the kinds of medical concerns raised by TGD people during the assessment are typically no different from those of any other surgical candidate.

Taking into consideration the mental and physical health disparities (Brown & Jones, 2016) and barriers to health care (Safer et al., 2016) experienced by TGD people, the assessment of physical conditions by HCPs should not be limited to a history of medical interventions. If the TGD person has physical health conditions, it is important these conditions are managed while initiating or continuing GAMSTs whenever possible. Any interruption in treatment should be made with a view toward re-initiating treatment as soon as practicable. It is also important HCPs develop a treatment strategy for managing physical conditions that facilitates health and promotes consistent adherence to a treatment plan.

Statement 5.3.f
Assess the capacity to consent for the specific gender-affirming treatments prior to the initiation of this treatment.

The practice of informed consent to treatment is central to the provision of health care. Informed consent is couched in the ethical principle that recipients of health care should understand the health care they receive and any potential consequences that could result. The importance of informed consent is embedded in many legislative and regulatory practices that guide HCPs around the world (Jefford & Moore, 2008). It is not possible to know all the potential consequences of a health care treatment; instead, considering what would be "reasonable" to expect is often used as a minimum criterion for consent (Jefford & Moore, 2008; Spatz et al., 2016) and remains the case with GAMSTs. Being able to consent to a health care procedure or clinical intervention requires several complex cognitive processes.

Consent requires the cognitive capacity to understand the risks and benefits of a treatment and the potential negative and positive outcomes in addition to the ability to retain that information for the purposes of making the decision (using aids as necessary) and the cognitive ability to use that understanding to make an informed decision (American Medical Association, 2021; Applebaum, 2007). It is vital the TGD person and the assessing HCP consider a priori the nature of the treatment sought and the potential positive and negative effects it may have on the biological, psychological, and social domains of the TGD person's life.

It is important to recognize mental illness, in particular symptoms of cognitive impairment or psychosis, can impact a person's ability to grant consent for GAMSTs (Hostiuc et al., 2018). However, the presence of such symptoms does not necessarily equate to an inability to give consent because many people with significant mental health symptoms are able to understand the risks and benefits of treatment enough to make an informed decision (Carpenter et al., 2000). Instead, it is important a careful assessment is carried out that examines each TGD person's ability to comprehend the nature of the specific GAMST being considered, consider treatment options, including risks and benefits, appreciate the potential short- and long-term consequences of the decision, and communicate their choice in order to receive the treatment (Grootens-Wiegers et al., 2017).

There may be instances in which an individual lacks the capacity to consent to health care, such as during an acute episode of psychosis or in situations where an individual has long-term cognitive impairment. However, limits to capacity to consent to treatment should not prevent individuals from receiving appropriate GAMSTs. For some, understanding the risks and benefits may require the use of repeated explanations in jargon-free language over time or the use of diagrams to facilitate explanation and aid comprehension. A comprehensive and thorough assessment undertaken by the multidisciplinary health care team can further inform this process. For others, an alternative decision maker, such as a legal guardian or regulator-approved,

independent decision maker may need to be appointed. These situations need to be considered on a case-by-case basis with the aim of ensuring the most affirmative and least restrictive health care is provided to the individual. Also see Chapter 11—Institutional Environments.

Statement 5.3.g

Assess the capacity of the gender diverse and transgender adult to understand the effect of gender-affirming treatment on reproduction and explore reproductive options with the individual prior to the initiation of gender-affirming treatment.

As gender-affirming medical interventions often affect reproductive capacity, HCPs should ensure a TGD person is aware of the implications for reproduction of the treatments and is familiar with gamete storage and assistive reproductive options. Gender-affirming hormone treatments have been shown to impact reproductive functions and fertility, although the consequences are heterogenous for people of all birth-assigned sexes (Adeleye et al., 2019; Jindarak et al., 2018; Taub et al., 2020). There may be individual differences and fluctuations in these effects on TGD adults. It is therefore essential that HCPs inform a TGD person about the possible impact of the treatment on their reproductive potential during the assessment and as part of the evaluation of the person's capacity to consent for GAMSTs. Reproductive options should be considered and discussed prior to the initiation of gender-affirming treatments. Because the literature is unclear about the possibility of conception while on hormone therapy, information about the necessity of using contraception to avoid unwanted pregnancy and the different methods of contraception available may need to be provided (Light et al., 2014; Schubert & Carey,2020).

Cross-sectional studies in clinical and nonclinical samples from different populations consistently report TGD adults express parental desire and wish to pursue fertility preservation with varying rates that are related to age, gender, and the duration of gender-affirming hormone treatment (Auer et al., 2018; De Sutter et al., 2002; Defreyne, Van Schuvlenbergh et al., 2020; Wierckx, Stuyver et al., 2012). In a small sample,

provision of fertility information was found to have an influence on decision-making related to the use of fertility preservation (Chen et al., 2019). Although there was no comparison made between groups who did and did not receive fertility counseling, high fertility preservation rates occurred following comprehensive fertility counseling among transgender individuals (Amir et al., 2020). Further, one study suggested consultation with a specialist reduced regret related to the decision about whether to pursue fertility preservation procedures (Vyas et al., 2021). For more information see Chapter 16—Reproductive Health.

Statement 5.4

We suggest, as part of the assessment for gender-affirming hormonal or surgical treatment, professionals who have competencies in the assessment of transgender and gender diverse people wishing gender-related medical treatment consider the role of social transition together with the individual.

Social transition can be extremely beneficial to many TGD people although not all TGD people are able to socially transition or wish to socially transition (Bränström & Pachankis, 2021; Koehler et al., 2018; Nieder, Eyssel et al., 2020). Consequently, some TGD people seek gender-affirming interventions after social transition, some before, some during, and some in the absence of social transition.

Social transition and gender identity disclosure can improve the mental health of a TGD person seeking gender-affirming interventions (Hughto et al., 2020; McDowell et al., 2019). In addition, chest and facial surgeries prior to hormone therapy can facilitate social transition (Altman, 2012; Davis & Colton Meier, 2014; Olson-Kennedy, Warus et al. 2018; Van Boerum et al., 2019). As part of the assessment process, HCPs should discuss which social role is most comfortable for the TGD person, if a social transition is planned, and the timing for any planned social transition (Barker & Wylie, 2008). It is imperative during the assessment process, HCPs are respectful of the wide diversity of gendered social roles, including nonbinary as well as binary identities and presentations, which vary

according to cultural, local community, and individual understandings.

Not everyone who requests GAMSTs will wish to or be able to socially transition. Little is known about TGD people who do not socially transition before, during, or after medical treatment, as this has not been systematically studied. The most frequent reasons that have been identified for avoiding social transition are fear of being abandoned by family or friends, fearing economic loss (Bradford et al., 2013), and being discriminated against and stigmatized (Langenderfer-Magruder et al., 2016; McDowell et al., 2019; White Hughto et al., 2015). However, some people do not pursue social transition because they feel hormonal or surgical treatments offer enough subjective improvement to reduce gender dysphoria.

If there is no clear plan for social transition or if social transition is unwanted, additional assessment is important to determine the specific nature and advisability of the treatment request, especially if surgical treatment is requested. Additional assessment can offer the TGD person an opportunity to consider the possible effects of not socially transitioning while still obtaining GAMSTs. Given the lack of data on health outcomes for TGD people who do not socially transition (Evans et al., 2021; Levine, 2009; Turban, Loo et al., 2021), GAMSTs should be approached cautiously in such circumstances.

Statement 5.5

We recommend transgender and gender diverse adults who fulfill the criteria for gender-affirming medical and surgical treatment require a single opinion for the initiation of this treatment from a professional who has competencies in the assessment of transgender and gender diverse people wishing gender-related medical and surgical treatment.

Previous versions of the SOC guidelines have required TGD individuals to be assessed for GAMSTs by two qualified HCPs. It was believed having two independent opinions was best practice as it ensured safety for both TGD people and HCPs. For example, it was assumed that seeing two HCPs offered assuredness for both TGD people and their assessing HCPs when pursuing irreversible medical interventions.

However, the limited research in the area indicates two opinions are largely unnecessary. For example, Jones, Brewin et al. (2017) reviewed the case notes of experienced HCPs working within a state-funded gender service and found there was an overwhelming correlation between both opinions—arguably making one of them redundant. Further, Bouman et al. (2014) determined the requirement for two independent assessors reflected paternalism in health care services and raised a potential breach of the autonomy of TGD individuals. The authors posited when clients are adequately prepared and assessed under the care of a multidisciplinary team, a second independent assessment is unnecessary.

Consequently, if written documentation or a letter is required to recommend gender-affirming medical and surgical treatment (GAMST), TGD people seeking treatments including hormones, and genital, chest, facial and other gender-affirming surgeries require a single written opinion/signature from an HCP competent to independently assess and diagnose (Bouman et al., 2014; Yuan et al, 2021). Further written opinions/signatures may be requested where there is a specific clinical need.

Statement 5.6

We suggest health care professionals assessing transgender and gender diverse people seeking gonadectomy consider a minimum of 6 months of hormone therapy as appropriate to the TGD person's gender goals before the TGD person undergoes irreversible surgical intervention (unless hormones are not clinically indicated for the individual).

The Endocrine Society Clinical Practice Guidelines advise a period of consistent hormone treatment prior to genital surgery (Hembree et al., 2017). While there was limited supportive research, this recommendation was considered to be good clinical practice as it allows a more reversible experience prior to the irreversible experience of surgery. For example, there can be changes in sexual desire after genital surgery that removes the testicles (Lawrence, 2005; Wierckx, Van de Peer et al., 2014). In this context, reversible testosterone suppression can offer a TGD person a period of time to experience the absence of testosterone and decide if this feels right for

them. It should be noted the effects of reduced estrogen on a TGD person's sexual desire and functioning following an oophorectomy is less well documented.

Surgery that removes gonads is an irreversible procedure that leads to loss of fertility and loss of the effects of endogenous sex steroids. Both effects must be discussed as a component of the assessment process. For additional information see Chapter 16—Reproductive Health. Of course, hormones are not clinically indicated for TGD adults who do not want them or in cases where they are contraindicated due to health reasons. For more information see Chapter 13—Surgery and Postoperative Care.

Statement 5.7

We recommend health care professionals assessing adults who wish to detransition and seek gender-related hormone intervention, surgical intervention, or both, utilize a comprehensive multidisciplinary assessment that will include additional viewpoints from experienced health care professionals in transgender health and that considers, together with the individual, the role of social transition as part of the assessment process.

Many TGD adults may consider a range of identities and elements of gender presentation while they are exploring their gender identity and are considering transition options. Accordingly, people may spend some time in a gender identity or presentation before they discover it does not feel comfortable and later adapt it or shift to an earlier identity or presentation (Turban, King et al., 2021). Some TGD adults may also experience a change in gender identity over time so that their needs for medical treatment evolve. This is a healthy and reasonable process for determining the most comfortable and congruent way of living, which is informed by the person's gender identity and the context of their life. This process of identity exploration should not necessarily be equated with regret, confusion, or poor decision-making because a TGD adult's gender identity may change without devaluing previous transition decisions (MacKinnon et al., 2021; Turban, Loo et al., 2021). TGD adults should be assisted in this exploration and any other changes

in their identity (Expósito-Campos, 2021). While exploration continues, gender-affirming treatments that are irreversible should be avoided until clarity about long-term goals and outcomes is achieved.

The decision to detransition appears to be rare (Defreyne, Motmans et al., 2017; Hadje-Moussa et al., 2019; Wiepjes et al., 2018). Estimates of the number of people who detransition due to a change in identity are likely to be overinflated due to research blending different cohorts (Expósito-Campos, 2021). For example, detransition research cohorts often include TGD adults who chose to detransition because of a change in their identity as well as TGD adults who chose to detransition without a change in identity. While little research has been conducted to systematically examine variables that correlate with a TGD adult's decision to halt a transition process or to detransition, a recent study found the vast majority of TGD people who opted to detransition did so due to external factors, such as stigma and lack of social support and not because of changes in gender identity (Turban, King et al., 2021). TGD adults who have not experienced a change in identity may choose to halt transition or to detransition because of oppression, violence, and social/relational conflict, surgical complications, health concerns, physical contraindications, a lack of resources, or dissatisfaction with the results (Expósito-Campos, 2021). In such cases, MHPs are well placed to assist the TGD person with these challenges.

While the choice to detransition is proportionally rare, it is expected an overall increase in the number of adults who identify as TGD would result in an increase in the absolute number of people seeking to halt or reverse a transition. However, while the absolute numbers may increase, the percentage of people seeking to halt or reverse permanent physical changes should remain static and low. The existence of these rare requests must not be used as a justification to interrupt critical, medically necessary care, including hormone and surgical treatments, for the vast majority of TGD adults.

Due to the limited research in this area, clinical guidance is based primarily on individual case studies and the expert opinion of HCPs

working with TGD adults (Expósito-Campos, 2021; Richards & Barrett, 2020). Accordingly, if a TGD adult has undergone permanent physical changes and seeks to undo them, the assessing HCP should be a member of a comprehensive multidisciplinary assessment team. A multidisciplinary team allows for the contribution of additional viewpoints from HCPs experienced in transgender health. In collaboration with the TGD adult, the multidisciplinary team is encouraged to thoroughly understand the motivations for the original treatment and for the decision to detransition. Any concerns with the previous physical changes should be carefully explored and a significant effort made to ensure similar concerns are not replicated by the reversal.

To ensure the greatest likelihood of satisfaction and comfort with a reversal of permanent physical changes, the TGD adult and the multidisciplinary team should explore the role of social transition in the assessment and in preparation for the reversal. In such instances, it is highly likely a prolonged period of living in role will be necessary before further physical changes are recommended. HCPs should support the TGD adult through any social changes, as well as any feelings of failure, shame, depression, or guilt in deciding to make such a change. In addition, people should be supported in coping with any prejudice or social difficulties they may have experienced that could have led to a decision to detransition or that may have resulted from such a decision. It is also important to help the person remain engaged with health care throughout the process (Narayan et al., 2021).

While available research shows consistent positive outcomes for the majority of TGD adults who choose to transition (Aldridge et al., 2020; Byne et al., 2012; Gorin-Lazard et al., 2012; Owen-Smith et al., 2018; White Hughto & Reisner, 2016), some TGD adults may decompensate or experience a worsened condition following transition. Little research has been conducted to systematically examine variables that correlate with poor or worsened biological, psychological, or social conditions following transition (Hall et al., 2021; Littman, 2021); however, this occurrence appears to be rare (Hall et al., 2021; Wiepjes et al., 2018). In cases where people decompensate after physical or social transition and then remain in a poorer biological, psychological, or social state than they were in prior to transition, serious consideration should be given as to whether transition is helpful at this time, for this person, or both. In cases where treatment is no longer supported, assistance should be arranged to support the person to manage the process of stopping treatment and to manage any concomitant difficulties (Narayan et al., 2021).

It is vital that people who detransition, for any reason, be supported. It should be remembered, however, this is a rare occurrence and the literature shows consistently positive outcomes for the vast majority of TGD adults who transition to a gender that is comfortable for them, including those who receive GAMSTs (Byne et al., 2012; Green & Fleming, 1990; Lawrence, 2003; Motmans et al., 2012; Van de Grift, Elaut et al., 2018).

CHAPTER 6 Adolescents

Historical context and changes since previous Standards of Care

Specialized health care for transgender adolescents began in the 1980s when a few specialized gender clinics for youth were developed around the world that served relatively small numbers of children and adolescents. In more recent years, there has been a sharp increase in the number of adolescents requesting gender care (Arnoldussen et al., 2019; Kaltiala, Bergman et al., 2020). Since then, new clinics have been founded, but clinical services in many places have not kept pace with the increasing number of youth seeking care. Hence, there are often long waitlists for services, and barriers to care exist for many transgender youth around the world (Tollit et al., 2018).

Until recently, there was limited information regarding the prevalence of gender diversity among adolescents. Studies from high school samples indicate much higher rates than earlier thought, with reports of up to 1.2% of participants identifying as transgender (Clark et al., 2014) and up to 2.7% or more (e.g., 7–9%) experiencing some level of self-reported gender diversity (Eisenberg et al., 2017; Kidd et al., 2021; Wang et al., 2020). These studies suggest gender diversity in youth should no longer be viewed as rare. Additionally, a pattern of uneven ratios by assigned sex has been reported in gender clinics, with adolescents assigned female at birth (AFAB) initiating care 2.5–7.1 times more frequently as compared to adolescents who are assigned male at birth (AMAB) (Aitken et al., 2015; Arnoldussen et al., 2019; Bauer et al., 2021; de Graaf, Carmichael et al., 2018; Kaltiala et al., 2015; Kaltiala, Bergman et al., 2020).

A specific World Professional Association for Transgender Health's (WPATH) Standards of Care section dedicated to the needs of children and adolescents was first included in the 1998 WPATH Standards of Care, 5th version (Levine et al., 1998). Youth aged 16 or older were deemed potentially eligible for gender-affirming medical care, but only in select cases. The subsequent 6th (Meyer et al., 2005) and 7th (Coleman et al., 2012) versions divided medical-affirming treatment for adolescents into three categories and presented eligibility criteria regarding age/puberty stage—namely fully reversible puberty delaying blockers as soon as puberty had started; partially reversible hormone therapy (testosterone, estrogen) for adolescents at the age of majority, which was age 16 in certain European countries; and irreversible surgeries at age 18 or older, except for chest "masculinizing" mastectomy, which had an age minimum of 16 years. Additional eligibility criteria for gender-related medical care included a persistent, long (childhood) history of gender "non-conformity"/dysphoria, emerging or intensifying at the onset of puberty; absence or management of psychological, medical, or social problems that interfere with treatment; provision of support for commencing the intervention by the parents/caregivers; and provision of informed consent. A chapter dedicated to transgender and gender diverse (TGD) adolescents, distinct from the child chapter, has been created for this 8th edition of the Standards of Care given 1) the exponential growth in adolescent referral rates; 2) the increased number of studies specific to adolescent gender diversity-related care; and 3) the unique developmental and gender-affirming care issues of this age group.

Non-specific terms for gender-related care are avoided (e.g., gender-affirming model, gender exploratory model) as these terms do not represent unified practices, but instead heterogenous care practices that are defined differently in various settings.

Adolescence overview

Adolescence is a developmental period characterized by relatively rapid physical and psychological maturation, bridging childhood and adulthood (Sanders, 2013). Multiple developmental processes occur simultaneously, including pubertal-signaled changes. Cognitive, emotional, and social systems mature, and physical changes associated with puberty progress. These processes do not all begin and end at the same time for a given individual, nor do they occur at the same age for all persons. Therefore, the lower and upper borders of adolescence are imprecise and cannot be defined exclusively by age. For example, physical pubertal changes may

begin in late childhood and executive control neural systems continue to develop well into the mid-20s (Ferguson et al., 2021). There is a lack of uniformity in how countries and governments define the age of majority (i.e., legal decision-making status; Dick et al., 2014). While many specify the age of majority as 18 years of age, in some countries it is as young as 15 years (e.g., Indonesia and Myanmar), and in others as high as 21 years (e.g., the U.S. state of Mississippi and Singapore).

For clarity, this chapter applies to adolescents from the start of puberty until the legal age of majority (in most cases 18 years), however there are developmental elements of this chapter, including the importance of parental/caregiver involvement, that are often relevant for the care of transitional-aged young adults and should be considered appropriately.

Cognitive development in adolescence is often characterized by gains in abstract thinking, complex reasoning, and metacognition (i.e., a young person's ability to think about their own feelings in relation to how others perceive them; Sanders, 2013). The ability to reason hypothetical situations enables a young person to conceptualize implications regarding a particular decision. However, adolescence is also often associated with increased risk-taking behaviors. Along with these notable changes, adolescence is often characterized by individuation from parents and the development of increased personal autonomy. There is often a heightened focus on peer relationships, which can be both positive and detrimental (Gardner & Steinberg, 2005). Adolescents often experience a sense of urgency that stems from hypersensitivity to reward, and their sense of timing has been shown to be different from that of older individuals (Van Leijenhorst et al., 2010). Social-emotional development typically advances during adolescence, although there is a great variability among young people in terms of the level of maturity applied to inter- and intra-personal communication and insight (Grootens-Wiegers et al., 2017). For TGD adolescents making decisions about gender-affirming treatments—decisions that may have lifelong consequences—it is critical to understand how all these aspects of development may impact decision-making for a given young person within their specific cultural context.

Gender identity development in adolescence

Our understanding of gender identity development in adolescence is continuing to evolve. When providing clinical care to gender diverse young people and their families, it is important to know what is and is not known about gender identity during development (Berenbaum, 2018). When considering treatments, families may have questions regarding the development of their adolescent's gender identity, and whether or not their adolescent's declared gender will remain the same over time. For some adolescents, a declared gender identity that differs from the assigned sex at birth comes as no surprise to their parents/caregivers as their history of gender diverse expression dates back to childhood (Leibowitz & de Vries, 2016). For others, the declaration does not happen until the emergence of pubertal changes or even well into adolescence (McCallion et al., 2021; Sorbara et al., 2020).

Historically, social learning and cognitive developmental research on gender development was conducted primarily with youth who were not gender diverse in identity or expression and was carried out under the assumption that sex correlated with a specific gender; therefore, little attention was given to gender identity development. In addition to biological factors influencing gender development, this research demonstrated psychological and social factors also play a role (Perry & Pauletti, 2011). While there has been less focus on gender identity development in TGD youth, there is ample reason to suppose, apart from biological factors, psychosocial factors are also involved (Steensma, Kreukels et al., 2013). For some youth, gender identity development appears fixed and is often expressed from a young age, while for others there may be a developmental process that contributes to gender identity development over time.

Neuroimaging studies, genetic studies, and other hormone studies in intersex individuals demonstrate a biological contribution to the development of gender identity for some

individuals whose gender identity does not match their assigned sex at birth (Steensma, Kreukels et al., 2013). As families often have questions about this very issue, it is important to note it is not possible to distinguish between those for whom gender identity may seem fixed from birth and those for whom gender identity development appears to be a developmental process. Since it is impossible to definitively delineate the contribution of various factors contributing to gender identity development for any given young person, a comprehensive clinical approach is important and necessary (see Statement 3). Future research would shed more light on gender identity development if conducted over long periods of time with diverse cohort groups. Conceptualization of gender identity by shifting from dichotomous (e.g., binary) categorization of male and female to a dimensional gender spectrum along a continuum (APA, 2013) would also be necessary.

Adolescence may be a critical period for the development of gender identity for gender diverse young people (Steensma, Kreukels et al., 2013). Dutch longitudinal clinical follow-up studies of adolescents with childhood gender dysphoria who received puberty suppression, gender-affirming hormones, or both, found that none of the youth in adulthood regretted the decisions they had taken in adolescence (Cohen-Kettenis & van Goozen, 1997; de Vries et al., 2014). These findings suggest adolescents who were comprehensively assessed and determined emotionally mature enough to make treatment decisions regarding gender- affirming medical care presented with stability of gender identity over the time period when the studies were conducted.

When extrapolating findings from the longer-term longitudinal Dutch cohort studies to present-day gender diverse adolescents seeking care, it is critical to consider the societal changes that have occurred over time in relation to TGD people. Given the increase in visibility of TGD identities, it is important to understand how increased awareness may impact gender development in different ways (Kornienko et al., 2016). One trend identified is that more young people are presenting to gender clinics with nonbinary identities (Twist & de Graaf, 2019). Another phenomenon occurring in clinical practice is the increased number of adolescents seeking care who have not seemingly experienced, expressed (or experienced and expressed) gender diversity during their childhood years. One researcher attempted to study and describe a specific form of later-presenting gender diversity experience (Littman, 2018). However, the findings of the study must be considered within the context of significant methodological challenges, including 1) the study surveyed parents and not youth perspectives; and 2) recruitment included parents from community settings in which treatments for gender dysphoria are viewed with scepticism and are criticized. However, these findings have not been replicated. For a select subgroup of young people, susceptibility to social influence impacting gender may be an important differential to consider (Kornienko et al., 2016). However, caution must be taken to avoid assuming these phenomena occur prematurely in an individual adolescent while relying on information from datasets that may have been ascertained with potential sampling bias (Bauer et al., 2022; WPATH, 2018). It is important to consider the benefits that social connectedness may have for youth who are linked with supportive people (Tuzun et al., 2022)(see Statement 4).

Given the emerging nature of knowledge regarding adolescent gender identity development, an individualized approach to clinical care is considered both ethical and necessary. As is the case in all areas of medicine, each study has methodological limitations, and conclusions drawn from research cannot and should not be universally applied to all adolescents. This is also true when grappling with common parental questions regarding the stability versus instability of a particular young person's gender identity development. While future research will help advance scientific understanding of gender identity development, there may always be some gaps. Furthermore, given the ethics of self-determination in care, these gaps should not leave the TGD adolescent without important and necessary care.

Research evidence of gender-affirming medical treatment for transgender adolescents

A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical

and surgical treatments (GAMSTs) (see medically necessary statement in the Global chapter, Statement 2.1), over time. Given the lifelong implications of medical treatment and the young age at which treatments may be started, adolescents, their parents, and care providers should be informed about the nature of the evidence base. It seems reasonable that decisions to move forward with medical and surgical treatments should be made carefully. Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible. A short narrative review is provided instead.

At the time of this chapter's writing, there were several longer-term longitudinal cohort follow-up studies reporting positive results of early (i.e., adolescent) medical treatment; for a significant period of time, many of these studies were conducted through one Dutch clinic (e.g., Cohen-Kettenis & van Goozen, 1997; de Vries, Steensma et al., 2011; de Vries et al., 2014; Smith et al., 2001, 2005). The findings demonstrated the resolution of gender dysphoria is associated with improved psychological functioning and body image satisfaction. Most of these studies followed a pre-post methodological design and compared baseline psychological functioning with outcomes after the provision of medical gender-affirming treatments. Different studies evaluated individual aspects or combinations of treatment interventions and included 1) gender-affirming hormones and surgeries (Cohen-Kettenis & van Goozen, 1997; Smith et al., 2001, 2005); 2) puberty suppression (de Vries, Steensma et al., 2011); and 3) puberty suppression, affirming hormones, and surgeries (de Vries et al., 2014). The 2014 long-term follow-up study is the only study that followed youth from early adolescence (pretreatment, mean age of 13.6) through young adulthood (posttreatment, mean age of 20.7). This was the first study to show gender-affirming treatment enabled transgender adolescents to make age-appropriate developmental transitions while living as their affirmed gender with satisfactory objective and subjective outcomes in adulthood (de Vries et al., 2014). While the study employed a small (n = 55), select, and socially supported sample, the results were convincing. Of note, the participants were part of the Dutch clinic known for employing a multidisciplinary approach, including provision of comprehensive, ongoing assessment and management of gender dysphoria, and support aimed at emotional well-being.

Several more recently published longitudinal studies followed and evaluated participants at different stages of their gender-affirming treatments. In these studies, some participants may not have started gender-affirming medical treatments, some had been treated with puberty suppression, while still others had started gender-affirming hormones or had even undergone gender-affirming surgery (GAS) (Achille et al., 2020; Allen et al., 2019; Becker-Hebly et al., 2021; Carmichael et al., 2021; Costa et al., 2015; Kuper et al., 2020, Tordoff et al., 2022). Given the heterogeneity of treatments and methods, this type of design makes interpreting outcomes more challenging. Nonetheless, when compared with baseline assessments, the data consistently demonstrate improved or stable psychological functioning, body image, and treatment satisfaction varying from three months to up to two years from the initiation of treatment.

Cross-sectional studies provide another design for evaluating the effects of gender-affirming treatments. One such study compared psychological functioning in transgender adolescents at baseline and while undergoing puberty suppression with that of cisgender high school peers at two different time points. At baseline, the transgender youth demonstrated lower psychological functioning compared with cisgender peers, whereas when undergoing puberty suppression, they demonstrated better functioning than their peers (van der Miesen et al., 2020). Grannis et al. (2021) demonstrated transgender males who started testosterone had lower internalizing mental health symptoms (depression and anxiety) compared with those who had not started testosterone treatment.

Four additional studies followed different outcome designs. In a retrospective chart study, Kaltiala, Heino et al. (2020) reported transgender

adolescents with few or no mental health challenges prior to commencing gender-affirming hormones generally did well during the treatment. However, adolescents with more mental health challenges at baseline continued to experience the manifestations of those mental health challenges over the course of gender-affirming medical treatment. Nieder et al. (2021) studied satisfaction with care as an outcome measure and demonstrated transgender adolescents were more satisfied the further they progressed with the treatments they initially started. Hisle-Gorman et al. (2021) compared health care utilization pre- and post-initiation of gender-affirming pharmaceuticals as indicators of the severity of mental health conditions among 3,754 TGD adolescents in a large health care data set. Somewhat contrary to the authors' hypothesis of improved mental health, mental health care use did not significantly change, and psychotropic medication prescriptions increased. In a large non-probability sample of transgender-identified adults, Turban et al. (2022) found those who reported access to gender-affirming hormones in adolescence had lower odds of past-year suicidality compared with transgender people accessing gender- affirming hormones in adulthood.

Providers may consider the possibility an adolescent may regret gender-affirming decisions made during adolescence, and a young person will want to stop treatment and return to living in the birth-assigned gender role in the future. Two Dutch studies report low rates of adolescents (1.9% and 3.5%) choosing to stop puberty suppression (Brik et al., 2019; Wiepjes et al., 2018). Again, these studies were conducted in clinics that follow a protocol that includes a comprehensive assessment before the gender-affirming medical treatment is started. At present, no clinical cohort studies have reported on profiles of adolescents who regret their initial decision or detransition after irreversible affirming treatment. Recent research indicate there are adolescents who detransition, but do not regret initiating treatment as they experienced the start of treatment as a part of understanding their gender-related care needs (Turban, 2018). However, this may not be the predominant perspective of people who

detransition (Littman, 2021; Vandenbussche, 2021). Some adolescents may regret the steps they have taken (Dyer, 2020). Therefore, it is important to present the full range of possible outcomes when assisting transgender adolescents. Providers may discuss this topic in a collaborative and trusting manner (i.e., as a "potential future experience and consideration") with the adolescent and their parents/caregivers before gender-affirming medical treatments are started. Also, providers should be prepared to support adolescents who detransition. In an internet convenience sample survey of 237 self-identified detransitioners with a mean age of 25.02 years, which consisted of over 90% of birth assigned females, 25% had medically transitioned before age 18 and 14% detransitioned before age 18 (Vandenbussche, 2021). Although an internet convenience sample is subject to selection of respondents, this study suggests detransitioning may occur in young transgender adolescents and health care professionals should be aware of this. Many of them expressed difficulties finding help during their detransition process and reported their detransition was an isolating experience during which they did not receive either sufficient or appropriate support (Vandenbussche, 2021).

To conclude, although the existing samples reported on relatively small groups of youth (e.g., n = 22-101 per study) and the time to follow-up varied across studies (6 months–7 years), this emerging evidence base indicates a general improvement in the lives of transgender adolescents who, following careful assessment, receive medically necessary gender-affirming medical treatment. Further, rates of reported regret during the study monitoring periods are low. Taken as a whole, the data show early medical intervention—as part of broader combined assessment and treatment approaches focused on gender dysphoria and general well-being—can be effective and helpful for many transgender adolescents seeking these treatments.

Ethical and human rights perspectives

Medical ethics and human rights perspectives were also considered while formulating the

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Statements of Recommendations

6.1- We recommend health care professionals working with gender diverse adolescents:

6.1.a- Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.

6.1.b- Receive theoretical and evidenced-based training and develop expertise in general child, adolescent, and family mental health across the developmental spectrum.

6.1.c- Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.

6.1.d- Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.

6.1.e- Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.

6.2- We recommend health care professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular identity is favored.

6.3- We recommend health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical/surgical transition-related care, and that this be accomplished in a collaborative and supportive manner.

6.4- We recommend health care professionals work with families, schools, and other relevant settings to promote acceptance of gender diverse expressions of behavior and identities of the adolescent.

6.5- We recommend against offering reparative and conversion therapy aimed at trying to change a person's gender and lived gender expression to become more congruent with the sex assigned at birth.

6.6- We suggest health care professionals provide transgender and gender diverse adolescents with health education on chest binding and genital tucking, including a review of the benefits and risks.

6.7- We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.

6.8- We recommend health care professionals maintain an ongoing relationship with the gender diverse and transgender adolescent and any relevant caregivers to support the adolescent in their decision-making throughout the duration of puberty suppression treatment, hormonal treatment, and gender- related surgery until the transition is made to adult care.

6.9- We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care.

6.10- We recommend health care professionals working with transgender and gender diverse adolescents requesting gender-affirming medical or surgical treatments inform them, prior to initiating treatment, of the reproductive effects including the potential loss of fertility and available options to preserve fertility within the context of the youth's stage of pubertal development.

6.11- We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or not feasible.

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (All of them must be met):

6.12- We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:

6.12.a- The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care. In countries that have not implemented the latest ICD, other taxonomies may be used although efforts should be undertaken to utilize the latest ICD as soon as practicable.

6.12.b- The experience of gender diversity/incongruence is marked and sustained over time.

6.12.c- The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.

6.12.d- The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed.

6.12.e- The adolescent has been informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.

6.12.f- The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.

6.12.g- The adolescent had at least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated.

adolescent SOC statements. For example, allowing irreversible puberty to progress in adolescents who experience gender incongruence is not a neutral act given that it may have immediate and lifelong harmful effects for the transgender young person (Giordano, 2009; Giordano & Holm, 2020; Kreukels & Cohen-Kettenis, 2011). From a human rights perspective, considering gender diversity as a normal and expected variation within the broader diversity of the human experience, it is an adolescent's right to participate in their own decision-making

process about their health and lives, including access to gender health services (Amnesty International, 2020).

Short summary of statements and unique issues in adolescence

These guidelines are designed to account for what is known and what is not known about gender identity development in adolescence, the evidence for gender-affirming care in adolescence, and the unique aspects that distinguish adolescence from other developmental stages.

> *Identity exploration*: A defining feature of adolescence is the solidifying of aspects of identity, including gender identity. Statement 6.2 addresses identity exploration in the context of gender identity development. Statement 6.12.b accounts for the length of time needed for a young person to experience a gender diverse identity, express a gender diverse identity, or both, so as to make a meaningful decision regarding gender-affirming care.

> *Consent and decision-making*: In adolescence, consent and decision-making require assessment of the individual's emotional, cognitive, and psychosocial development. Statement 6.12.c directly addresses emotional and cognitive maturity and describes the necessary components of the evaluation process used to assess decision-making capacity.

> *Caregivers/parent involvement*: Adolescents are typically dependent on their caregivers/parents for guidance in numerous ways. This is also true as the young person navigates through the process of deciding about treatment options. Statement 6.11 addresses the importance of involving caregivers/parents and discusses the role they play in the assessment and treatment. No set of guidelines can account for every set of individual circumstances on a global scale.

Statement 6.1

We recommend health care professionals working with gender diverse adolescents:

a. Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.
b. Receive theoretical and evidenced-based training and develop expertise in general

child, adolescent, and family mental health across the developmental spectrum.
c. Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.
d. Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.
e. Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.

When assessing and supporting TGD adolescents and their families, care providers/health care professionals (HCPs) need both general as well as gender-specific knowledge and training. Providers who are trained to work with adolescents and families play an important role in navigating aspects of adolescent development and family dynamics when caring for youth and families (Adelson et al., 2012; American Psychological Association, 2015; Hembree et al., 2017). Other chapters in these standards of care describe these criteria for professionals who provide gender care in more detail (see Chapter 5—Assessment for Adults; Chapter 7—Children; or Chapter 13—Surgery and Postoperative Care). Professionals working with adolescents should understand what is and is not known regarding adolescent gender identity development, and how this knowledge base differs from what applies to adults and prepubertal children. Among HCPs, the mental health professional (MHP) has the most appropriate training and dedicated clinical time to conduct an assessment and elucidate treatment priorities and goals when working with transgender youth, including those seeking gender-affirming medical/surgical care. Understanding and managing the dynamics of family members who may share differing perspectives regarding the history and needs of the

young person is an important competency that MHPs are often most prepared to address.

When access to professionals trained in child and adolescent development is not possible, HCPs should make a commitment to obtain training in the areas of family dynamics and adolescent development, including gender identity development. Similarly, considering autistic/neurodivergent transgender youth represent a substantial minority subpopulation of youth served in gender clinics globally, it is important HCPs seek additional training in the field of autism and understand the unique elements of care autistic gender diverse youth may require (Strang, Meagher et al., 2018). If these qualifications are not possible, then consultation and collaboration with a provider who specializes in autism and neurodiversity is advised.

Statement 6.2

We recommend health care professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular identity is favored.

Adolescence is a developmental period that involves physical and psychological changes characterized by individuation and the transition to independence from caregivers (Berenbaum et al., 2015; Steinberg, 2009). It is a period during which young people may explore different aspects of identity, including gender identity.

Adolescents differ regarding the degree to which they explore and commit to aspects of their identity (Meeus et al., 2012). For some adolescents, the pace to achieving consolidation of identity is fast, while for others it is slower. For some adolescents, physical, emotional, and psychological development occur over the same general timeline, while for others, there are certain gaps between these aspects of development. Similarly, there is variation in the timeline for gender identity development (Arnoldussen et al., 2020; Katz-Wise et al., 2017). For some young people, gender identity development is a clear process that starts in early childhood, while for others pubertal changes contribute to a person's experience of themselves as a particular gender (Steensma, Kreukels et al., 2013), and for many others a process may begin well after pubertal

changes are completed. Given these variations, there is no one particular pace, process, or outcome that can be predicted for an individual adolescent seeking gender-affirming care.

Therefore, HCPs working with adolescents should promote supportive environments that simultaneously respect an adolescent's affirmed gender identity and also allows the adolescent to openly explore gender needs, including social, medical, and physical gender-affirming interventions should they change or evolve over time.

Statement 6.3

We recommend health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical/surgical transition-related care, and that this be accomplished in a collaborative and supportive manner.

Given the many ways identity may unfold during adolescence, we recommend using a comprehensive biopsychosocial assessment to guide treatment decisions and optimize outcomes. This assessment should aim to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care. As mentioned in Statement 6.1, MHPs have the most appropriate training, experience, and dedicated clinical time required to obtain the information discussed here. The assessment process should be approached collaboratively with the adolescent and their caregiver(s), both separately and together, as described in more detail in Statement 6.11. An assessment should occur prior to any medically necessary medical or surgical intervention under consideration (e.g., puberty blocking medication, gender-affirming hormones, surgeries). See medically necessary statement in Chapter 2—Global Applicability, Statement 2.1; see also Chapter 12—Hormone Therapy and Chapter 13—Surgery and Postoperative Care.

Youth may experience many different gender identity trajectories. Sociocultural definitions and experiences of gender continue to evolve over time, and youth are increasingly presenting with a range of identities and ways of describing their experiences and gender-related needs (Twist & de

Graaf, 2019). For example, some youth will realize they are transgender or more broadly gender diverse and pursue steps to present accordingly. For some youth, obtaining gender-affirming medical treatment is important while for others these steps may not be necessary. For example, a process of exploration over time might not result in the young person self-affirming or embodying a different gender in relation to their assigned sex at birth and would not involve the use of medical interventions (Arnoldussen et al., 2019).

The most robust longitudinal evidence supporting the benefits of gender-affirming medical and surgical treatments in adolescence was obtained in a clinical setting that incorporated a detailed comprehensive diagnostic assessment process over time into its delivery of care protocol (de Vries & Cohen-Kettenis, 2012; de Vries et al., 2014). Given this research and the ongoing evolution of gender diverse experiences in society, a comprehensive diagnostic biopsychosocial assessment during adolescence is both evidence-based and preserves the integrity of the decision-making process. In the absence of a full diagnostic profile, other mental health entities that need to be prioritized and treated may not be detected. There are no studies of the long-term outcomes of gender-related medical treatments for youth who have not undergone a comprehensive assessment. Treatment in this context (e.g., with limited or no assessment) has no empirical support and therefore carries the risk that the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time.

As delivery of health care and access to specialists varies globally, designing a particular assessment process to adapt existing resources is often necessary. In some cases, a more extended assessment process may be useful, such as for youth with more complex presentations (e.g., complicating mental health histories (Leibowitz & de Vries, 2016)), co-occurring autism spectrum characteristics (Strang, Powers et al., 2018), and/or an absence of experienced childhood gender incongruence (Ristori & Steensma, 2016). Given the unique cultural, financial, and geographical factors that exist for specific populations, providers should design assessment models that are flexible and allow for appropriately timed care for as many young people as possible, so long as the assessment effectively obtains information about the adolescent's strengths, vulnerabilities, diagnostic profile, and individual needs. Psychometrically validated psychosocial and gender measures can also be used to provide additional information.

The multidisciplinary assessment for youth seeking gender-affirming medical/surgical interventions includes the following domains that correspond to the relevant statements:

- **Gender Identity Development:** Statements 6.12.a and 6.12.b elaborate on the factors associated with gender identity development within the specific cultural context when assessing TGD adolescents.
- **Social Development and Support; Intersectionality:** Statements 6.4 and 6.11 elaborate on the importance of assessing gender minority stress, family dynamics, and other aspects contributing to social development and intersectionality.
- **Diagnostic Assessment of Possible Co-Occurring Mental Health and/or Developmental Concerns:** Statement 6.12.d elaborates on the importance of understanding the relationship that exists, if at all, between any co-occurring mental health or developmental concerns and the young person's gender identity/gender diverse expression.
- **Capacity for Decision-Making:** Statement 6.12.c elaborates on the assessment of a young person's emotional maturity and the relevance when an adolescent is considering gender affirming-medical/surgical treatments.

Statement 6.4
We recommend health care professionals work with families, schools, and other relevant settings to promote acceptance of gender diverse expressions of behavior and identities of the adolescent.

Multiple studies and related expert consensus support the implementation of approaches that promote acceptance and affirmation of gender diverse youth across all settings, including families, schools, health care facilities, and all other organizations and communities with which they

interact (e.g., Pariseau et al., 2019; Russell et al., 2018; Simons et al., 2013; Toomey et al., 2010; Travers et al., 2012). Acceptance and affirmation are accomplished through a range of approaches, actions, and policies we recommend be enacted across the various relationships and settings in which a young person exists and functions. It is important for the family members and community members involved in the adolescent's life to work collaboratively in these efforts unless their involvement is considered harmful to the adolescent. Examples proposed by Pariseau et al. (2019) and others of acceptance and affirmation of gender diversity and contemplation and expression of identity that can be implemented by family, staff, and organizations include:

1. Actions that are supportive of youth drawn to engaging in gender-expansive (e.g., nonconforming) activities and interests;
2. Communications that are supportive when youth express their experiences about their gender and gender exploration;
3. Use of the youth's asserted name/pronouns;
4. Support for youth wearing clothing/uniforms, hairstyles, and items (e.g., jewelry, makeup) they feel affirm their gender;
5. Positive and supportive communication with youth about their gender and gender concerns;
6. Education about gender diversity issues for people in the young person's life (e.g., family members, health care providers, social support networks), as needed, including information about how to advocate for gender diverse youth in community, school, health care, and other settings;
7. Support for gender diverse youth to connect with communities of support (e.g., LGBTQ groups, events, friends);
8. Provision of opportunities to discuss, consider, and explore medical treatment options when indicated;
9. Antibullying policies that are enforced;
10. Inclusion of nonbinary experiences in daily life, reading materials, and curricula (e.g., books, health, and sex education classes, assigned essay topics that move beyond the binary, LGBTQ, and ally groups);

11. Gender inclusive facilities that the youth can readily access without segregation from nongender diverse peers (e.g., bathrooms, locker rooms).

We recommend HCPs work with parents, schools, and other organizations/groups to promote acceptance and affirmation of TGD identities and expressions, whether social or medical interventions are implemented or not as acceptance and affirmation are associated with fewer negative mental health and behavioral symptoms and more positive mental health and behavioral functioning (Day et al., 2015; de Vries et al., 2016; Greytak et al., 2013; Pariseau et al., 2019; Peng et al., 2019; Russell et al., 2018; Simons et al., 2013; Taliaferro et al., 2019; Toomey et al., 2010; Travers et al., 2012). Russell et al. (2018) found mental health improvement increases with more acceptance and affirmation across more settings (e.g., home, school, work, and friends). Rejection by family, peers, and school staff (e.g., intentionally using the name and pronoun the youth does not identify with, not acknowledging affirmed gender identity, bullying, harassment, verbal and physical abuse, poor relationships, rejection for being TGD, eviction) was strongly linked to negative outcomes, such as anxiety, depression, suicidal ideation, suicide attempts, and substance use (Grossman et al., 2005; Klein & Golub; 2016; Pariseau et al., 2019; Peng et al., 2019; Reisner, Greytak et al., 2015; Roberts et al., 2013). It is important to be aware that negative symptoms increase with increased levels of rejection and continue into adulthood (Roberts et al., 2013).

Neutral or indifferent responses to a youth's gender diversity and exploration (e.g., letting a child tell others their chosen name but not using the name, not telling family or friends when the youth wants them to disclose, not advocating for the child about rejecting behavior from school staff or peers, not engaging or participating in other support mechanisms (e.g., with psychotherapists and support groups) have also been found to have negative consequences, such as increased depressive symptoms (Pariseau et al., 2019). For these reasons, it is important not to ignore a youth's gender questioning or delay consideration of the youth's gender-related

care needs. There is particular value in professionals recognizing youth need individualized approaches, support, and consideration of needs around gender expression, identity, and embodiment over time and across domains and relationships. Youth may need help coping with the tension of tolerating others' processing/adjusting to an adolescent's identity exploration and changes (e.g., Kuper, Lindley et al., 2019). It is important professionals collaborate with parents and others as they process their concerns and feelings and educate themselves about gender diversity because such processes may not necessarily reflect rejection or neutrality but may rather represent efforts to develop attitudes and gather information that foster acceptance (e.g., Katz-Wise et al., 2017).

Statement 6.5

We recommend against offering reparative and conversion therapy aimed at trying to change a person's gender and lived gender expression to become more congruent with the sex assigned at birth.

Some health care providers, secular or religious organizations, and rejecting families may undertake efforts to thwart an adolescent's expression of gender diversity or assertion of a gender identity other than the expression and behavior that conforms to the sex assigned at birth. Such efforts at blocking reversible social expression or transition may include choosing not to use the youth's identified name and pronouns or restricting self-expression in clothing and hairstyles (Craig et al., 2017; Green et al., 2020). These disaffirming behaviors typically aim to reinforce views that a young person's gender identity/expression must match the gender associated with the sex assigned at birth or expectations based on the sex assigned at birth. Activities and approaches (sometimes referred to as "treatments") aimed at trying to change a person's gender identity and expression to become more congruent with the sex assigned at birth have been attempted, but these approaches have not resulted in changes in gender identity (Craig et al., 2017; Green et al., 2020). We recommend against such efforts because they have been found to be ineffective

and are associated with increases in mental illness and poorer psychological functioning (Craig et al., 2017; Green et al., 2020; Turban, Beckwith et al., 2020).

Much of the research evaluating "conversion therapy" and "reparative therapy" has investigated the impact of efforts to change gender expression (masculinity or femininity) and has conflated sexual orientation with gender identity (APA, 2009; Burnes et al., 2016; Craig et al., 2017). Some of these efforts have targeted both gender identity and expression (AACAP, 2018). Conversion/reparative therapy has been linked to increased anxiety, depression, suicidal ideation, suicide attempts, and health care avoidance (Craig et al., 2017; Green et al., 2020; Turban, Beckwith et al., 2020). Although some of these studies have been criticized for their methodologies and conclusions (e.g., D'Angelo et al., 2020), this should not detract from the importance of emphasizing efforts undertaken a priori to change a person's identity are clinically and ethically unsound. We recommend against any type of conversion or attempts to change a person's gender identity because 1) both secular and religion-based efforts to change gender identity/expression have been associated with negative psychological functioning that endures into adulthood (Turban, Beckwith et al., 2020); and 2) larger ethical reasons exist that should underscore respect for gender diverse identities.

It is important to note potential factors driving a young person's gender-related experience and report of gender incongruence, when carried out in the context of supporting an adolescent with self-discovery, is not considered reparative therapy as long as there is no a priori goal to change or promote one particular gender identity or expression (AACAP, 2018; see Statement 6.2). To ensure these explorations are therapeutic, we recommend employing affirmative consideration and supportive tone in discussing what steps have been tried, considered, and planned for a youth's gender expression. These discussion topics may include what felt helpful or affirming, what felt unhelpful or distressing and why. We recommend employing affirmative responses to these steps and discussions, such as those identified in SOC-8 Statement 6.4.

Statement 6.6

We suggest health care professionals provide transgender and gender diverse adolescents with health education on chest binding and genital tucking, including review of the benefits and risks.

TGD youth may experience distress related to chest and genital anatomy. Practices such as chest binding, chest padding, genital tucking, and genital packing are reversible, nonmedical interventions that may help alleviate this distress (Callen-Lorde, 2020a, 2020b; Deutsch, 2016a; Olson-Kennedy, Rosenthal et al., 2018; Transcare BC, 2020). It is important to assess the degree of distress related to physical development or anatomy, educate youth about potential nonmedical interventions to address this distress, and discuss the safe use of these interventions.

Chest binding involves compression of the breast tissue to create a flatter appearance of the chest. Studies suggest that up to 87% of trans masculine patients report a history of binding (Jones, 2015; Peitzmeier, 2017). Binding methods may include the use of commercial binders, sports bras, layering of shirts, layering of sports bras, or the use of elastics or other bandages (Peitzmeier, 2017). Currently, most youth report learning about binding practices from online communities composed of peers (Julian, 2019). Providers can play an important role in ensuring youth receive accurate and reliable information about the potential benefits and risks of chest binding. Additionally, providers can counsel patients about safe binding practices and monitor for potential negative health effects. While there are potential negative physical impacts of binding, youth who bind report many benefits, including increased comfort, improved safety, and lower rates of misgendering (Julian, 2019). Common negative health impacts of chest binding in youth include back/chest pain, shortness of breath, and overheating (Julian, 2019). More serious negative health impacts such as skin infections, respiratory infections, and rib fractures are uncommon and have been associated with chest binding in adults (Peitzmeier, 2017). If binding is employed, youth should be advised to use only those methods considered safe for binding—such as binders specifically designed for the gender diverse population—to reduce the risk of serious negative health effects. Methods that are considered unsafe for binding include the use of duct tape, ace wraps, and plastic wrap as these can restrict blood flow, damage skin, and restrict breathing. If youth report negative health impacts from chest binding, these should ideally be addressed by a gender-affirming medical provider with experience working with TGD youth.

Genital tucking is the practice of positioning the penis and testes to reduce the outward appearance of a genital bulge. Methods of tucking include tucking the penis and testes between the legs or tucking the testes inside the inguinal canal and pulling the penis back between the legs. Typically, genitals are held in place by underwear or a gaff, a garment that can be made or purchased. Limited studies are available on the specific risks and benefits of tucking in adults, and none have been carried out in youth. Previous studies have reported tight undergarments are associated with decreased sperm concentration and motility. In addition, elevated scrotal temperatures can be associated with poor sperm characteristics, and genital tucking could theoretically affect spermatogenesis and fertility (Marsh, 2019) although there are no definitive studies evaluating these adverse outcomes. Further research is needed to determine the specific benefits and risks of tucking in youth.

Statement 6.7

We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.

When discussing the available options of menstrual-suppressing medications with gender diverse youth, providers should engage in shared decision-making, use gender-inclusive language (e.g., asking patients which terms they utilize to refer to their menses, reproductive organs, and genitalia) and perform physical exams in a sensitive, gender-affirmative manner (Bonnington et al., 2020; Krempasky et al., 2020). There is no formal research evaluating how menstrual

suppression may impact gender incongruence and/or dysphoria. However, the use of menstrual suppression can be an initial intervention that allows for further exploration of gender-related goals of care, prioritization of other mental health care, or both, especially for those who experience a worsening of gender dysphoria from unwanted uterine bleeding (see Statement 6.12d; Mehringer & Dowshen, 2019). When testosterone is not used, menstrual suppression can be achieved via a progestin. To exclude any underlying menstrual disorders, it is important to obtain a detailed menstrual history and evaluation prior to implementing menstrual-suppressing therapy (Carswell & Roberts, 2017). As part of the discussion about menstrual-suppressing medications, the need for contraception and information regarding the effectiveness of menstrual-suppressing medications as methods of contraception also need to be addressed (Bonnington et al., 2020). A variety of menstrual suppression options, such as combined estrogen-progestin medications, oral progestins, depot and subdermal progestin, and intrauterine devices (IUDs), should be offered to allow for individualized treatment plans while properly considering availability, cost and insurance coverage, as well as contraindications and side effects (Kanj et al., 2019).

Progestin-only hormonal medication are options, especially in trans masculine or nonbinary youth who are not interested in estrogen-containing medical therapies as well as those at risk for thromboembolic events or who have other contraindications to estrogen therapy (Carswell & Roberts, 2017). Progestin-only hormonal medications include oral progestins, depo-medroxyprogesterone injection, etonogestrel implant, and levonorgestrel IUD (Schwartz et al., 2019). Progestin-only hormonal options vary in terms of efficacy in achieving menstrual suppression and have lower rates of achieving amenorrhea than combined oral contraception (Pradhan & Gomez-Lobo, 2019). A more detailed description of the relevant clinical studies is presented in Chapter 12—Hormone Therapy. HCPs should not make assumptions regarding the individual's preferred method of administration as some trans masculine youth may prefer vaginal rings or IUD implants (Akgul et al., 2019). Although hormonal

medications require monitoring for potential mood lability, depressive effects, or both, the benefits and risks of untreated menstrual suppression in the setting of gender dysphoria should be evaluated on an individual basis. Some patients may opt for combined oral contraception that includes different combinations of ethinyl estradiol, with ranging doses, and different generations of progestins (Pradhan & Gomez-Lobo, 2019). Lower dose ethinyl estradiol components of combined oral contraceptive pills are associated with increased breakthrough uterine bleeding. Continuous combined oral contraceptives may be used to allow for continuous menstrual suppression and can be delivered as transdermal or vaginal rings.

The use of gonadotropin releasing hormone (GnRH) analogues may also result in menstrual suppression. However, it is recommended gender diverse youth meet the eligibility criteria (as outlined in Statement 6.12) before this medication is considered solely for this purpose (Carswell & Roberts, 2017; Pradhan & Gomez-Lobo, 2019). Finally, menstrual-suppression medications may be indicated as an adjunctive therapy for breakthrough uterine bleeding that may occur while on exogenous testosterone or as a bridging medication while awaiting menstrual suppression with testosterone therapy. When exogenous testosterone is employed as a gender-affirming hormone, menstrual suppression is typically achieved in the first six months of therapy (Ahmad & Leinung, 2017). However, it is vital adolescents be counseled ovulation and pregnancy can still occur in the setting of amenorrhea (Gomez et al., 2020; Kanj et al., 2019).

Statement 6.8

We recommend health care professionals maintain an ongoing relationship with the gender diverse and transgender adolescent and any relevant caregivers to support the adolescent in their decision-making throughout the duration of puberty suppression treatment, hormonal treatment, and gender-related surgery until the transition is made to adult care.

HCPs with expertise in child and adolescent development, as described in Statement 6.1, play an important role in the continuity of care for

young people over the course of their gender-related treatment needs. Supporting adolescents and their families necessitates approaching care using a developmental lens through which understanding a young person's evolving emotional maturity and care needs can take place over time. As gender-affirming treatment pathways differ based on the needs and experiences of individual TGD adolescents, decision-making for these treatments (puberty suppression, estrogens/androgens, gender-affirmation surgeries) can occur at different points in time within a span of several years. Longitudinal research demonstrating the benefits of pubertal suppression and gender-affirming hormone treatment (GAHT) was carried out in a setting where an ongoing clinical relationship between the adolescents/families and the multidisciplinary team was maintained (de Vries et al., 2014).

Clinical settings that offer longer appointment times provide space for adolescents and caregivers to share important psychosocial aspects of emotional well-being (e.g., family dynamics, school, romantic, and sexual experiences) that contextualize individualized gender-affirming treatment needs and decisions as described elsewhere in the chapter. An ongoing clinical relationship can take place across settings, whether that be within a multidisciplinary team or with providers in different locations who collaborate with one another. Given the wide variability in the ability to obtain access to specialized gender care centers, particularly for marginalized groups who experience disparities with access, it is important for the HCP to appreciate the existence of any barriers to care while maintaining flexibility when defining how an ongoing clinical relationship can take place in that specific context.

An ongoing clinical relationship that increases resilience in the youth and provides support to parents/caregivers who may have their own treatment needs may ultimately lead to increased parental acceptance—when needed—which is associated with better mental health outcomes in youth (Ryan, Huebner et al., 2009).

Statement 6.9

We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care.

TGD adolescents with gender dysphoria/gender incongruence who seek gender-affirming medical and surgical treatments benefit from the involvement of health care professionals (HCPs) from different disciplines. Providing care to TGD adolescents includes addressing 1) diagnostic considerations (see Statements 6.3, 6.12a, and 6.12b) conducted by a specialized gender HCP (as defined in Statement 6.1) whenever possible and necessary; and 2) treatment considerations when prescribing, managing, and monitoring medications for gender-affirming medical and surgical care, requiring the training of the relevant medical/surgical professional. The list of key disciplines includes but is not limited to adolescent medicine/primary care, endocrinology, psychology, psychiatry, speech/language pathology, social work, support staff, and the surgical team.

The evolving evidence has shown a clinical benefit for transgender youth who receive their gender-affirming treatments in multidisciplinary gender clinics (de Vries et al., 2014; Kuper et al., 2020; Tollit et al., 2019). Finally, adolescents seeking gender-affirming care in multidisciplinary clinics are presenting with significant complexity necessitating close collaboration between mental health, medical, and/or surgical professionals (McCallion et al., 2021; Sorbara et al., 2020; Tishelman et al., 2015).

As not all patients and families are in the position or in a location to access multidisciplinary care, the lack of available disciplines should not preclude a young person from accessing needed care in a timely manner. When disciplines are available, particularly in centers with existing multidisciplinary teams, disciplines, or both, it is recommended efforts be made to include the relevant providers when developing a gender care team. However, this does not mean all disciplines are necessary to provide care to a particular youth and family.

If written documentation or a letter is required to recommend gender-affirming medical and surgical treatment (GAMST) for an adolescent, only one letter of assessment from a member of the multidisciplinary team is needed. This letter needs to reflect the assessment and opinion from the team that involves both medical HCPs and MHPs (American Psychological Association, 2015; Hembree et al., 2017; Telfer et al., 2018). Further assessment results and written opinions may be requested when there is a specific clinical need or when team members are in different locations or choose to write their own summaries. For further information see Chapter 5—Assessment for Adults, Statement 5.5.

Statement 6.10

We recommend health care professionals working with transgender and gender diverse adolescents requesting gender-affirming medical or surgical treatments inform them, prior to the initiation of treatment, of the reproductive effects, including the potential loss of fertility and available options to preserve fertility within the context of the youth's stage of pubertal development.

While assessing adolescents seeking gender-affirming medical or surgical treatments, HCPs should discuss the specific ways in which the required treatment may affect reproductive capacity. Fertility issues and the specific preservation options are more thoroughly discussed in Chapter 12—Hormone Therapy and Chapter 16—Reproductive Health.

It is important HCPs understand what fertility preservation options exist so they can relay the information to adolescents. Parents are advised to be involved in this process and should also understand the pros and cons of the different options. HCPs should acknowledge adolescents and parents may have different views around reproductive capacity and may therefore come to different decisions (Quain et al., 2020), which is why HCPs can be helpful in guiding this process.

HCPs should specifically pay attention to the developmental and psychological aspects of fertility preservation and decision-making competency for the individual adolescent. While adolescents may think they have made up their minds concerning their reproductive capacity, the possibility their opinions about having biologically related children in the future might change over time needs to be discussed with an HCP who has sufficient experience, is knowledgeable about adolescent development, and has experience working with parents.

Addressing the long-term consequences on fertility of gender-affirming medical treatments and ensuring transgender adolescents have realistic expectations concerning fertility preservation options or adoption cannot not be addressed with a one-time discussion but should be part of an ongoing conversation. This conversation should occur not only before initiating any medical intervention (puberty suppression, hormones, or surgeries), but also during further treatment and during transition.

Currently, there are only preliminary results from retrospective studies evaluating transgender adults and the decisions they made when they were young regarding the consequences of medical-affirming treatment on reproductive capacity. It is important not to make assumptions about what future adult goals an adolescent may have. Research in childhood cancer survivors found participants who acknowledged missed opportunities for fertility preservation reported distress and regret surrounding potential infertility (Armuand et al., 2014; Ellis et al., 2016; Lehmann et al., 2017). Furthermore, individuals with cancer who did not prioritize having biological children before treatment have reported "changing their minds" in survivorship (Armuand et al., 2014).

Given the complexities of the different fertility preservation options and the challenges HCPs may experience discussing fertility with the adolescent and the family (Tishelman et al., 2019), a fertility consultation is an important consideration for every transgender adolescent who pursues medical-affirming treatments unless the local situation is such that a fertility consultation is not covered by insurance or public health care plans, is not available locally, or the individual circumstances make this unpreferable.

Statement 6.11

We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents

involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or not feasible.

When there is an indication an adolescent might benefit from a gender-affirming medical or surgical treatment, involving the parent(s) or primary caregiver(s) in the assessment process is recommended in almost all situations (Edwards-Leeper & Spack, 2012; Rafferty et al., 2018). Exceptions to this might include situations in which an adolescent is in foster care, child protective services, or both, and custody and parent involvement would be impossible, inappropriate, or harmful. Parent and family support of TGD youth is a primary predictor of youth well-being and is protective of the mental health of TGD youth (Gower, Rider, Coleman et al., 2018; Grossman et al., 2019; Lefevor et al., 2019; McConnell et al., 2015; Pariseau et al., 2019; Ryan, 2009; Ryan et al., 2010; Simons et al., 2013; Wilson et al., 2016). Therefore, including parent(s)/caregiver(s) in the assessment process to encourage and facilitate increased parental understanding and support of the adolescent may be one of the most helpful practices available.

Parent(s)/caregiver(s) may provide key information for the clinical team, such as the young person's gender and overall developmental, medical, and mental health history as well as insights into the young person's level of current support, general functioning, and well-being. Concordance or divergence of reports given by the adolescent and their parent(s)/caregiver(s) may be important information for the assessment team and can aid in designing and shaping individualized youth and family supports (De Los Reyes et al., 2019; Katz-Wise et al., 2017). Knowledge of the family context, including resilience factors and challenges, can help providers know where special supports would be needed during the medical treatment process. Engagement of parent(s)/caregiver(s) is also important for educating families about various treatment approaches, ongoing follow-up and care needs, and potential treatment complications. Through psychoeducation regarding clinical gender care options and participation in the assessment process, which may unfold over time, parent(s)/caregiver(s) may better understand their adolescent

child's gender-related experience and needs (Andrzejewski et al., 2020; Katz-Wise et al., 2017).

Parent/caregiver concerns or questions regarding the stability of gender-related needs over time and implications of various gender-affirming interventions are common and should not be dismissed. It is appropriate for parent(s)/caregiver(s) to ask these questions, and there are cases in which the parent(s)/caregiver(s)' questions or concerns are particularly helpful in informing treatment decisions and plans. For example, a parent/caregiver report may provide critical context in situations in which a young person experiences very recent or sudden self-awareness of gender diversity and a corresponding gender treatment request, or when there is concern for possible excessive peer and social media influence on a young person's current self-gender concept. Contextualization of the parent/caregiver report is also critical, as the report of a young person's gender history as provided by parent(s)/caregiver(s) may or may not align with the young person's self-report. Importantly, gender histories may be unknown to parent(s)/caregiver(s) because gender may be internal experience for youth, not known by others unless it is discussed. For this reason, an adolescent's report of their gender history and experience is central to the assessment process.

Some parents may present with unsupportive or antagonistic beliefs about TGD identities, clinical gender care, or both (Clark et al., 2020). Such unsupportive perspectives are an important therapeutic target for families. Although challenging parent perspectives may in some cases seem rigid, providers should not assume this is the case. There are many examples of parent(s)/caregiver(s) who, over time with support and psychoeducation, have become increasingly accepting of their TGD child's gender diversity and care needs.

Helping youth and parent(s)/caregiver(s) work together on important gender care decisions is a primary goal. However, in some cases, parent(s)/caregiver(s) may be too rejecting of their adolescent child and their child's gender needs to be part of the clinical evaluation process. In these situations, youth may require the engagement of larger systems of advocacy and support to move

forward with the necessary support and care (Dubin et al., 2020).

Statement 6.12

We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:

Statement 6.12.a

The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care. In countries that have not implemented the latest ICD, other taxonomies may be used although efforts should be undertaken to utilize the latest ICD as soon as practicable.

When working with TGD adolescents, HCPs should realize while a classification may give access to care, pathologizing transgender identities may be experienced as stigmatizing (Beek et al., 2016). Assessments related to gender health and gender diversity have been criticized, and controversies exist around diagnostic systems (Drescher, 2016).

HCPs should assess the overall gender-related history and gender care-related needs of youth. Through this assessment process, HCPs may provide a diagnosis when it is required to get access to transgender-related care.

Gender incongruence and gender dysphoria are the two diagnostic terms used in the World Health Organization's International Classification of Diseases (ICD) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), respectively. Of these two widely used classification systems, the DSM is for psychiatric classifications only and the ICD contains all diseases and conditions related to physical as well as mental health. The most recent versions of these two systems, the DSM-5 and the ICD-11, reflect a long history of reconceptualizing and de-psychopathologizing gender-related diagnoses (American Psychiatric Association, 2013; World Health Organization, 2019a). Compared with the earlier version, the DSM-5 replaced gender identity disorder with gender dysphoria, acknowledging the distress experienced by some people stemming from the incongruence between experienced gender identity and the sex assigned at birth. In the most recent revision, the DSM-5-TR, no changes in the diagnostic criteria for gender dysphoria are made. However, terminology was adapted into the most appropriate current language (e.g., birth-assigned gender instead of natal-gender and gender-affirming treatment instead of gender reassignment (American Psychiatric Association, 2022). Compared with the ICD 10th edition, the gender incongruence classification was moved from the Mental Health chapter to the Conditions Related to Sexual Health chapter in the ICD-11. When compared with the DSM-5 classification of gender dysphoria, one important reconceptualization is distress is not a required indicator of the ICD-11 classification of gender incongruence (WHO, 2019a). After all, when growing up in a supporting and accepting environment, the distress and impairment criterion, an inherent part of every mental health condition, may not be applicable (Drescher, 2012). As such, the ICD-11 classification of gender incongruence may better capture the fullness of gender diversity experiences and related clinical gender needs.

Criteria for the ICD-11 classification gender incongruence of adolescence or adulthood require a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a need to "transition" to live and be accepted as a person of the experienced gender. For some, this includes hormonal treatment, surgery, or other health care services to enable the individual's body to align as much as required, and to the extent possible, with the person's experienced gender. Relevant for adolescents is the indicator that a classification cannot be assigned "prior to the onset of puberty." Finally, it is noted "that gender variant behaviour and preferences alone are not a basis for assigning the classification" (WHO, ICD-11, 2019a).

Criteria for the DSM-5 and DSM-5-TR classification of gender dysphoria in adolescence and adulthood denote "a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration' (criterion A, fulfilled when 2 of 6 subcriteria are manifest; DSM-5, APA, 2013; DSM 5-TR, APA, 2022).

Of note, although a gender-related classification is one of the requirements for receiving medical gender-affirming care, such a classification alone does not indicate a person needs medical-affirming care. The range of youth experiences of gender incongruence necessitates professionals provide a range of treatments or interventions based on the individual's needs. Counseling, gender exploration, mental health assessment and, when needed, treatment with MHPs trained in gender development may all be indicated with or without the implementation of medical-affirming care.

Statement 6.12.b

The experience of gender diversity/incongruence is marked and sustained over time.

Identity exploration and consolidation are experienced by many adolescents (Klimstra et al., 2010; Topolewska-Siedzik & Cieciuch, 2018). Identity exploration during adolescence may include a process of self-discovery around gender and gender identity (Steensma, Kreukels et al., 2013). Little is known about how processes that underlie consolidation of gender identity during adolescence (e.g., the process of commitment to specific identities) may impact a young person's experience(s) or needs over time.

Therefore, the level of reversibility of a gender-affirming medical intervention should be considered along with the sustained duration of a young person's experience of gender incongruence when initiating treatment. Given potential shifts in gender-related experiences and needs during adolescence, it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones or surgeries. Puberty suppression treatment, which provides more time for younger adolescents to engage their decision-making capacities, also raises important considerations (see Statement 6.12f and Chapter 12—Hormone Therapy) suggesting the importance of a sustained experience of gender incongruence/diversity prior to initiation. However, in this age group of younger adolescents, several years is not always practical nor necessary given the premise of the treatment as a means to buy time while avoiding distress from irreversible pubertal changes. For youth who have experienced a shorter duration of gender incongruence, social transition-related and/or other medical supports (e.g., menstrual suppression/androgen blocking) may also provide some relief as well as furnishing additional information to the clinical team regarding a young person's broad gender care needs (see Statements 6.4, 6.6, and 6.7).

Establishing evidence of persistent gender diversity/incongruence typically requires careful assessment with the young person over time (see Statement 6.3). Whenever possible and when appropriate, the assessment and discernment process should also include the parent(s)/caregiver(s) (see Statement 6.11). Evidence demonstrating gender diversity/incongruence sustained over time can be provided via history obtained directly from the adolescent and parents/caregivers when this information is not documented in the medical records.

The research literature on continuity versus discontinuity of gender-affirming medical care needs/requests is complex and somewhat difficult to interpret. A series of studies conducted over the last several decades, including some with methodological challenges (as noted by Temple Newhook et al., 2018; Winters et al., 2018) suggest the experience of gender incongruence is not consistent for all children as they progress into adolescence. For example, a subset of youth who experienced gender incongruence or who socially transitioned prior to puberty over time can show a reduction in or even full discontinuation of gender incongruence (de Vries et al., 2010; Olson et al., 2022; Ristori & Steensma, 2016; Singh et al., 2021; Wagner et al., 2021). However, there has been less research focused on rates of continuity and discontinuity of gender incongruence and gender-related needs in pubertal and adolescent populations. The data available regarding broad unselected gender-referred pubertal/adolescent cohorts (from the Amsterdam transgender clinic) suggest that, following extended assessments over time, a subset of adolescents with gender incongruence presenting for gender care elect not to pursue gender-affirming medical care

(Arnoldussen et al., 2019; de Vries, Steensma et al., 2011). Importantly, findings from studies of gender incongruent pubertal/adolescent cohorts, in which participants who have undergone comprehensive gender evaluation over time, have shown persistent gender incongruence and gender-related need and have received referrals for medical gender care, suggest low levels of regret regarding gender-related medical care decisions (de Vries et al., 2014; Wiepjes et al., 2018). Critically, these findings of low regret can only currently be applied to youth who have demonstrated sustained gender incongruence and gender-related needs over time as established through a comprehensive and iterative assessment (see Statement 6.3).

Statement 6.12.c

The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.

The process of informed consent includes communication between a patient and their provider regarding the patient's understanding of a potential intervention as well as, ultimately, the patient's decision whether to receive the intervention. In most settings, for minors, the legal guardian is integral to the informed consent process: if a treatment is to be given, the legal guardian (often the parent[s]/caregiver[s]) provides the informed consent to do so. In most settings, assent is a somewhat parallel process in which the minor and the provider communicate about the intervention and the provider assesses the level of understanding and intention.

A necessary step in the informed consent/ assent process for considering gender-affirming medical care is a careful discussion with qualified HCPs trained to assess the emotional and cognitive maturity of adolescents. The reversible and irreversible effects of the treatment, as well as fertility preservation options (when applicable), and all potential risks and benefits of the intervention are important components of the discussion. These discussions are required when obtaining informed consent/assent. Assessment of cognitive and emotional maturity is important because it helps the care team understand the adolescent's capacity to be informed.

The skills necessary to assent/consent to any medical intervention or treatment include the ability to 1) comprehend the nature of the treatment; 2) reason about treatment options, including the risks and benefits; 3) appreciate the nature of the decision, including the long-term consequences; and 4) communicate choice (Grootens-Wiegers et al., 2017). In the case of gender- affirming medical treatments, a young person should be well-informed about what the treatment may and may not accomplish, typical timelines for changes to appear (e.g., with gender-affirming hormones), and any implications of stopping the treatment. Gender-diverse youth should fully understand the reversible, partially reversible, and irreversible aspects of a treatment, as well as the limits of what is known about certain treatments (e.g., the impact of pubertal suppression on brain development (Chen and Loshak, 2020)). Gender-diverse youth should also understand, although many gender-diverse youth begin gender- affirming medical care and experience that care as a good fit for them long-term, there is a subset of individuals who over time discover this care is not a fit for them (Wiepjes et al., 2018). Youth should know such shifts are sometimes connected to a change in gender needs over time, and in some cases, a shift in gender identity itself. Given this information, gender diverse youth must be able to reason thoughtfully about treatment options, considering the implications of the choices at hand. Furthermore, as a foundation for providing assent, the gender-diverse young person needs to be able to communicate their choice.

The skills needed to accomplish the tasks required for assent/consent may not emerge at specific ages per se (Grootens-Wiegers et al., 2017). There may be variability in these capacities related to developmental differences and mental health presentations (Shumer & Tishelman, 2015) and dependent on the opportunities a young person has had to practice these skills (Alderson, 2007). Further, assessment of emotional and cognitive maturity must be conducted separately for each gender-related treatment decision (Vrouenraets et al., 2021).

The following questions may be useful to consider in assessing a young person's emotional and

cognitive readiness to assent or consent to a specific gender-affirming treatment:

- Can the young person think carefully into the future and consider the implications of a partially or fully irreversible intervention?
- Does the young person have sufficient self-reflective capacity to consider the possibility that gender-related needs and priorities can develop over time, and gender-related priorities at a certain point in time might change?
- Has the young person, to some extent, thought through the implications of what they might do if their priorities around gender do change in the future?
- Is the young person able to understand and manage the day-to-day short- and long-term aspects of a specific medical treatment (e.g., medication adherence, administration, and necessary medical follow-ups)?

Assessment of emotional and cognitive maturity may be accomplished over time as the care team continues to engage in conversations about the treatment options and affords the young person the opportunity to practice thinking into the future and flexibly consider options and implications. For youth with neurodevelopmental and/or some types of mental health differences, skills for future thinking, planning, big picture thinking, and self-reflection may be less-well developed (Dubbelink & Geurts, 2017). In these cases, a more careful approach to consent and assent may be required, and this may include additional time and structured opportunities for the young person to practice the skills necessary for medical decision-making (Strang, Powers et al., 2018).

For unique situations in which an adolescent minor is consenting for their own treatment without parental permission (see Statement 6.11), extra care must be taken to support the adolescent's informed decision-making. This will typically require greater levels of engagement of and collaboration between the HCPs working with the adolescent to provide the young person appropriate cognitive and emotional support to

consider options, weigh benefits and potential challenges/costs, and develop a plan for any needed (and potentially ongoing) supports associated with the treatment.

Statement 6.12.d

The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and/or gender-affirming medical treatments have been addressed.

Evidence indicates TGD adolescents are at increased risk of mental health challenges, often related to family/caregiver rejection, non-affirming community environments, and neurodiversity-related factors (e.g., de Vries et al., 2016; Pariseau et al., 2019; Ryan et al., 2010; Weinhardt et al., 2017). A young person's mental health challenges may impact their conceptualization of their gender development history and gender identity-related needs, the adolescent's capacity to consent, and the ability of the young person to engage in or receive medical treatment. Additionally, like cisgender youth, TGD youth may experience mental health concerns irrespective of the presence of gender dysphoria or gender incongruence. In particular, depression and self-harm may be of specific concern; many studies reveal depression scores and emotional and behavioral problems comparable to those reported in populations referred to mental health clinics (Leibowitz & de Vries, 2016). Higher rates of suicidal ideation, suicide attempts, and self-harm have also been reported (de Graaf et al., 2020). In addition, eating disorders occur more frequently than expected in non-referred populations (Khatchadourian et al., 2013; Ristori et al., 2019; Spack et al., 2012). Importantly, TGD adolescents show high rates of autism spectrum disorder/characteristics (Øien et al., 2018; van der Miesen et al., 2016; see also Statement 6.1d). Other neurodevelopmental presentations and/or mental health challenges may also be present, (e.g., ADHD, intellectual disability, and psychotic disorders (de Vries, Doreleijers et al., 2011; Meijer et al., 2018; Parkes & Hall, 2006).

Of note, many transgender adolescents are well-functioning and experience few if any mental health concerns. For example, socially transitioned pubertal adolescents who receive medical

gender- affirming treatment at specialized gender clinics may experience mental health outcomes equivalent to those of their cisgender peers (e.g., de Vries et al., 2014; van der Miesen et al., 2020). A provider's key task is to assess the direction of the relationships that exist between any mental health challenges and the young person's self-understanding of gender care needs and then prioritize accordingly.

Mental health difficulties may challenge the assessment and treatment of gender-related needs of TGD adolescents in various ways:

1. First, when a TGD adolescent is experiencing acute suicidality, self-harm, eating disorders, or other mental health crises that threaten physical health, safety must be prioritized. According to the local context and existing guidelines, appropriate care should seek to mitigate the threat or crisis so there is sufficient time and stabilization for thoughtful gender-related assessment and decision-making. For example, an actively suicidal adolescent may not be emotionally able to make an informed decision regarding gender-affirming medical/surgical treatment. If indicated, safety-related interventions should not preclude starting gender-affirming care.

2. Second, mental health can also complicate the assessment of gender development and gender identity-related needs. For example, it is critical to differentiate gender incongruence from specific mental health presentations, such as obsessions and compulsions, special interests in autism, rigid thinking, broader identity problems, parent/child interaction difficulties, severe developmental anxieties (e.g., fear of growing up and pubertal changes unrelated to gender identity), trauma, or psychotic thoughts. Mental health challenges that interfere with the clarity of identity development and gender-related decision-making should be prioritized and addressed.

3. Third, decision-making regarding gender-affirming medical treatments that have life-long consequences requires thoughtful, future-oriented thinking by the adolescent, with support from the parents/caregivers, as indicated (see Statement 6.11). To be able to make such an informed decision, an adolescent should be able to understand the issues, express a choice, appreciate and give careful thought regarding the wish for medical-affirming treatment (see Statement 6.12c). Neurodevelopmental differences, such as autistic features or autism spectrum disorder (see Statement 6.1d, e.g., communication differences; a preference for concrete or rigid thinking; differences in self-awareness, future thinking and planning), may challenge the assessment and decision-making process; neurodivergent youth may require extra support, structure, psychoeducation, and time built into the assessment process (Strang, Powers et al., 2018). Other mental health presentations that involve reduced communication and self-advocacy, difficulty engaging in assessment, memory and concentration difficulties, hopelessness, and difficulty engaging in future-oriented thinking may complicate assessment and decision-making. In such cases, extended time is often necessary before any decisions regarding medical-affirming treatment can be made.

4. Finally, while addressing mental health concerns is important during the course of medical treatment, it does not mean all mental health challenges can or should be resolved completely. However, it is important any mental health concerns are addressed sufficiently so that gender-affirming medical treatment can be provided optimally (e.g., medication adherence, attending follow-up medical appointments, and self-care, particularly during a postoperative course).

Statement 6.12.e

The adolescent has been informed of the reproductive effects, including the potential loss of fertility, and available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.

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For guidelines regarding the clinical approach, the scientific background, and the rationale, see Chapter 12—Hormone Therapy and Chapter 16—Reproductive Health.

Statement 6.12.f

The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.

The onset of puberty is a pivotal point for many gender diverse youth. For some, it creates an intensification of their gender incongruence, and for others, pubertal onset may lead to gender fluidity (e.g., a transition from binary to nonbinary gender identity) or even attenuation of a previously affirmed gender identity (Drummond et al., 2008; Steensma et al., 2011, Steensma, Kreukels et al., 2013; Wallien & Cohen-Kettenis, 2008). The use of puberty-blocking medications, such as GnRH analogues, is not recommended until children have achieved a minimum of Tanner stage 2 of puberty because the experience of physical puberty may be critical for further gender identity development for some TGD adolescents (Steensma et al., 2011). Therefore, puberty blockers should not be implemented in prepubertal gender diverse youth (Waal & Cohen-Kettenis, 2006). For some youth, GnRH agonists may be appropriate in late stages or in the post-pubertal period (e.g., Tanner stage 4 or 5), and this should be highly individualized. See Chapter 12—Hormone Therapy for a more comprehensive review of the use of GnRH agonists.

Variations in the timing of pubertal onset is due to multiple factors (e.g., sex assigned at birth, genetics, nutrition, etc.). Tanner staging refers to five stages of pubertal development ranging from prepubertal (Tanner stage 1) to post-pubertal, and adult sexual maturity (Tanner stage 5) (Marshall & Tanner, 1969, 1970). For assigned females at birth, pubertal onset (e.g., gonadarche) is defined by the occurrence of breast budding (Tanner stage 2), and for birth-assigned males, the achievement of a testicular volume of greater than or equal to 4 mL (Roberts & Kaiser, 2020). An experienced medical provider should be relied on to differentiate the onset of puberty from physical changes such as pubic hair and apocrine body odor due to sex steroids produced by the adrenal gland (e.g., adrenarche) as adrenarche does not warrant the use of puberty-blocking medications (Roberts & Kaiser, 2020). Educating parents and families about the difference between adrenarche and gonadarche helps families understand the timing during which shared decision-making about gender-affirming medical therapies should be undertaken with their multidisciplinary team.

The importance of addressing other risks and benefits of pubertal suppression, both hypothetical and actual, cannot be overstated. Evidence supports the existence of surgical implications for transgender girls who proceed with pubertal suppression (van de Grift et al., 2020). Longitudinal data exists to demonstrate improvement in romantic and sexual satisfaction for adolescents receiving puberty suppression, hormone treatment and surgery (Bungener et al., 2020). A study on surgical outcomes of laparoscopic intestinal vaginoplasty (performed because of limited genital tissue after the use of puberty blockers) in transgender women revealed that the majority experienced orgasm after surgery (84%), although a specific correlation between sexual pleasure outcomes and the timing of pubertal suppression initiation was not discussed in the study (Bouman, van der Sluis et al., 2016), nor does the study apply to those who would prefer a different surgical procedure. This underscores the importance of engaging in discussions with families about the future unknowns related to surgical and sexual health outcomes.

Statement 6.12.g

The adolescent had at least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated.

GAHT leads to anatomical, physiological, and psychological changes. The onset of the anatomic effects (e.g., clitoral growth, breast growth, vaginal mucosal atrophy) may begin early after the initiation of therapy, and the peak effect is expected at 1–2 years (T'Sjoen et al., 2019). To

ensure sufficient time for psychological adaptations to the physical change during an important developmental time for the adolescent, 12 months of hormone treatment is suggested. Depending upon the surgical result required, a period of hormone treatment may need to be longer (e.g., sufficient clitoral virilization prior to metoidioplasty/phalloplasty, breast growth and skin expansion prior to breast augmentation, softening of skin and changes in facial fat distribution prior to facial GAS) (de Blok et al., 2021).

For individuals who are not taking hormones prior to surgical interventions, it is important surgeons review the impact of hormone therapy on the proposed surgery. In addition, for individuals undergoing gonadectomy who are not taking hormones, a plan for hormone replacement can be developed with their prescribing professional prior to surgery.

Consideration of ages for gender-affirming medical and surgical treatment for adolescents

Age has a strong, albeit imperfect, correlation with cognitive and psychosocial development and may be a useful objective marker for determining the potential timing of interventions (Ferguson et al., 2021). Higher (i.e., more advanced) ages may be required for treatments with greater irreversibility, complexity, or both. This approach allows for continued cognitive/emotional maturation that may be required for the adolescent to fully consider and consent to increasingly complex treatments (see Statement 6.12c).

A growing body of evidence indicates providing gender-affirming treatment for gender diverse youth who meet criteria leads to positive outcomes (Achille et al., 2020; de Vries et al., 2014; Kuper et al., 2020). There is, however, limited data on the optimal timing of gender-affirming interventions as well as the long-term physical, psychological, and neurodevelopmental outcomes in youth (Chen et al., 2020; Chew et al., 2018; Olson-Kennedy et al., 2016). Currently, the only existing longitudinal studies evaluating gender diverse youth and adult outcomes are based on a specific model (i.e., the Dutch approach) that involved a comprehensive initial assessment with follow-up. In this approach, pubertal suppression was considered at age 12, GAHT at age 16, and surgical interventions after age 18 with exceptions in some cases. It is not clear if deviations from this approach would lead to the same or different outcomes. Longitudinal studies are currently underway to better define outcomes as well as the safety and efficacy of gender-affirming treatments in youth (Olson-Kennedy, Garofalo et al., 2019; Olson-Kennedy, Rosenthal et al., 2019). While the long-term effects of gender-affirming treatments initiated in adolescence are not fully known, the potential negative health consequences of delaying treatment should also be considered (de Vries et al., 2021). As the evidence base regarding outcomes of gender-affirming interventions in youth continues to grow, recommendations on the timing and readiness for these interventions may be updated.

Previous guidelines regarding gender-affirming treatment of adolescents recommended partially reversible GAHT could be initiated at approximately 16 years of age (Coleman et al., 2012; Hembree et al., 2009). More recent guidelines suggest there may be compelling reasons to initiate GAHT prior to the age of 16, although there are limited studies on youth who have initiated hormones prior to 14 years of age (Hembree et al., 2017). A compelling reason for earlier initiation of GAHT, for example, might be to avoid prolonged pubertal suppression, given potential bone health concerns and the psychosocial implications of delaying puberty as described in more detail in Chapter 12—Hormone Therapy (Klink, Caris et al., 2015; Schagen et al., 2020; Vlot et al., 2017; Zhu & Chan, 2017). Puberty is a time of significant brain and cognitive development. The potential neurodevelopmental impact of extended pubertal suppression in gender diverse youth has been specifically identified as an area in need of continued study (Chen et al., 2020). While GnRH analogs have been shown to be safe when used for the treatment of precocious puberty, there are concerns delaying exposure to sex hormones (endogenous or exogenous) at a time of peak bone mineralization may lead to decreased bone mineral density. The potential decrease in bone mineral density as well as the clinical significance of any decrease requires continued study (Klink, Caris et al., 2015; Lee, Finlayson et al.,

CERTIFICATE OF SERVICE

I certify that I e-filed this appendix on ECF, which will email everyone requiring

notice.

Dated: October 13, 2023   /s/ Mohammad O. Jazil