No. 23-12159

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

Jane Doe et al.,
Plaintiffs-Appellees,

v.

Surgeon General, State of Florida et al.,
Defendants-Appellants.

U.S. District Court for the Northern District of Florida, No. 4:23-cv-114
(Hinkle, J.)

APPELLANTS' APPENDIX – VOLUME XI OF XIII

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INDEX TO APPENDIX

10	Doc.193-10, DX10	The Cass Review, Independent Review of Gender Identity Services for Children and Young People
10-11	Doc.193-11, DX11	National Institute for Health and Care Excellence, Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria
11	Doc.193-12, DX12	National Institute for Health and Care Excellence, Evidence Review: Gender-Affirming Hormones for Children and Adolescents with Gender Dysphoria
11	Doc.193-13, DX13	France's Academie Nationale de Medecine Press Release
11	Doc.193-14, DX14	The Royal Australian and New Zealand College of Psychiatrists' Position Statement on Gender-Affirming Care
11-12	Doc.193-16, DX16	WPATH Standards of Care, Version 8
12-13	Doc.193-17, DX17	WPATH Standards-of-Care-Revision Team Criteria
13	Doc.193-24, DX24	Endocrine Society Guidelines on Treatments for Gender Dysphoria

Dated: September 13, 2023

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Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	years), respectively at commencement of GnRH analogues. Of the 143 adolescents in the study, 125 (87%, 36 transfemales and 89 transmales) subsequently started treatment with gender-affirming hormones after median 1.0 (range 0.5 to 3.8) years and 0.8 (0.3 to 3.7) years, respectively. Median age at the start of gender-affirming hormones was 16.2 years (range 14.5 to 18.6 years) in transfemales and 17.1 years (range 14.9 to 18.8 years) in transmales. Five adolescents who used GnRH analogues had not started gender-affirming hormones at the time of data collection as they were not yet eligible for this treatment due to age. At the time of data collection, they had used GnRH analogues for a median duration of 2.1 years (range 1.6 to 2.8). Tanner stage was not reported. Six adolescents had been referred to a gender clinic elsewhere for further		• 1 transmale experienced mood swings 4 months after commencing GnRH analogues. After 2.2 years he developed unexplained severe nausea and rapid weight loss and due to his general condition discontinued GnRH analogues after 2.4 years[3] • 1 transmale stopped GnRH analogues as his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections[4] Five adolescents (3.5%) stopped treatment as they no longer wished to continue with gender-affirming treatment. • 1 adolescent had been very distressed about breast development at the start of GnRH analogues and later thought that she might want to live as a woman without breasts. She did not want to live as a boy and discontinued GnRH analogues, although dreaded breast development and menstruation. • 1 adolescent experienced concurrent psychosocial problems interfering with the exploration of gender identity and did not currently want treatment.[5] • 1 adolescent felt more in between male and female and therefore did not want to continue with GnRH analogues.[6] • 1 adolescent made a social transition while using GnRH analogues and shortly after decided to discontinue treatment.[7]	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	treatment, including 1 who had prolonged use.		• 1 adolescent discontinued after using GnRH analogues as the treatment allowed them to feel who they were.[8]	

[1] The adolescent later indicated "I was already fully matured when I started GnRH analogues, menstruations were already suppressed by contraceptives. For me, it had no added value" (transmale, age 19 years).
[2] The adolescent restarted endocrine treatment (testosterone) 5 months later.
[3] The adolescent recovered over the next 2 years and subsequently started lynestrenol and testosterone treatment.
[4] The adolescent subsequently started lynestrenol to suppress menses, he was not yet eligible for testosterone treatment.
[5] The adolescent later reflected that "The decision to stop GnRH analogues to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment" (adolescent assigned female sex at birth, age 16 years).
[6] The adolescent stated "At the moment, I feel more like 'I am' instead of 'I am a woman' or 'I am a man'" (adolescent assigned female sex at birth, age 16 years).
[7] The adolescent stated that "he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.
[8] The adolescent stated "After using GnRH analogues for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman" (adolescent assigned female sex at birth, age 18 years).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Costa R, Dunsford M, Skagerberg E, et al. (2015) Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. Journal of Sexual Medicine 12(11):2206-14. United Kingdom Prospective longitudinal observational single centre cohort study Includes participants referred to the service between 2010 and 2014.	Adolescents with gender dysphoria who completed a 6-month diagnostic process using DSM-IV-TR criteria for gender dysphoria (comprising the gender dysphoria assessment and psychological interventions) either immediately eligible for treatment with GnRH analogues or delayed eligible for treatment with GnRH analogues (received psychological support without any physical intervention). No exclusion criteria were reported. The sample consisted of 201 adolescents (sex assigned at birth male to female ratio 1:1.6) mean (±SD) age 15.52±1.41 years) from a sampling frame of	**Intervention** 101 individuals were assessed as being immediately eligible for use of GnRH analogues (no specific treatment, dose or route, or frequency of administration reported but all received psychological support). **Comparison** The analyses were between the immediately eligible and delayed eligible (n=100) adolescents,	**Critical outcomes** ***Impact on gender dysphoria*** The Utrecht gender dysphoria scale (UGDS) was used to assess adolescents' gender dysphoria related discomfort. The Cronbach's alpha (α) for the study was reported as 0.76 to 0.88, suggesting good internal consistency. UGDS was only reported once, for 160 adolescents (50 sex assigned at birth males and 110 sex assigned at birth females). The assessment time point is not reported (baseline or follow-up) and the comparison for gender related discomfort was between sex assigned at birth males and sex assigned at birth females. Sex assigned at birth males had a mean (±SD) UGDS score of 51.6 [±9.7] versus sex assigned at birth females score of 56.1 [±4.3], *t*-test 4.07; p<0.001.	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. drawn from the same community as the exposed cohort. 3. secure record 4. no **Domain 2: Comparability** 1. partial comparator **Domain 3: Outcome** 1. independent assessment (unclear if blinded) 2. yes 3. incomplete follow-up **Overall quality is assessed as poor.**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	436 consecutive adolescents referred to the service between 2010 and 2014. The mean (±SD) age (n=201) at the start of GnRH analogues was 16.48 [±1.26], range 13 to 17 years. The interval from the start of the diagnostic procedure to the start of puberty suppression took approximately 1.5 years [±0.63] from baseline. None of the delayed eligible individuals received puberty suppression at the time of this study. Tanner stage was not reported.	Baseline assessment (following diagnostic procedure) was followed by follow-up at 6 months from baseline (T1), 12 months from baseline (T2) and 18 months from baseline (T3).	***Impact on mental health*** Not assessed. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Psychosocial impact*** The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS was administered by psychologists, psychotherapists, and psychiatrists (intra-class correlation assessment was 0.76 ≤ Cronbach's α ≤0.94). At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and sex assigned at birth females (all p>0.1). In comparison with sex assigned at birth females, sex assigned at birth males had statistically significantly lower mean (±SD) baseline CGAS scores (55.4 [±12.7] versus 59.2 [11.8]; *t*-test 2.15; p=0.03). There was no statistically significant difference in mean (±SD) CGAS scores at baseline (T0) between immediately eligible adolescents and delayed eligible adolescents (n=201, 58.72 [±11.38] versus 56.63 [±13.14]; *t*-test 1.21; p=0.23). **Immediately eligible compared with delayed eligible participants** At follow-up, there was no statistically significant difference in mean (±SD) CGAS scores at any follow-up time point (T1, T2 or T3) between immediately	Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Large unexplained loss to follow-up (64.7%) at T3. Source of funding: not reported.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			eligible adolescents and delayed eligible adolescents: • T1, n=201, 60.89 [±12.17] versus 60.29 [±12.81]; *t*-test 0.34; p=0.73 • T2, n=121, 64.70 [±13.34] versus 62.97 [±14.10]; *t*-test 0.69; p=0.49 • T3, n=71, 67.40 [±13.93] versus 62.53 [±13.54]; *t*-test 1.49; p=0.14. **All participants** There was a statistically significant increase in mean (±SD) CGAS scores at any follow-up time point (T1, T2 or T3) compared with baseline (T0) for the all adolescents group: • T0 (n=201) versus T1 (n=201), 57.73 [±12.27] versus 60.68 [±12.47]; *t*-test 4.87; p<0.001 • T0 (n=201) versus T2 (n=121), 57.73 [±12.27] versus 63.31 [±14.41]; *t*-test 3.70; p<0.001 • T0 (n=201) versus T3 (n=71), 57.73 [±12.27] versus 64.93 [±13.85]; *t*-test 4.11; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 but not for the periods T1 to T2 and T2 to T3, for all adolescents: • T1 (n=201) versus T2 (n=121), 60.68 [±12.47] versus 63.31 [±14.41]; *t*-test 1.73; p<0.08 • T1 (n=201) versus T3 (n=71), 60.68 [±12.47] versus 64.93 [±13.85], *t*-test 2.40; p<0.02 • T2 (n=121) versus T3 (n=71), 63.31 [±14.41] versus 64.93 [±13.85], *t*-test 0.76; p=0.45 There were no statistically significant differences in CGAS scores between sex assigned at birth males and sex	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			assigned at birth females with gender dysphoria in all the follow-up evaluations (all p>0.1). Delayed eligible and immediately eligible adolescents with gender dysphoria were not statistically significantly different for demographic variables (all p>0.1). **Immediately eligible participants** There was a statistically significant increase in mean (±SD) CGAS scores at follow-up times T2 and T3 compared with baseline (T0) but not for T0 versus T1, for the immediately eligible adolescents: • T0 (n=101) versus T1 (n=101), 58.72 [±11.38] versus 60.89 [±12.17]; *t*-test 1.31; p=0.19 • T0 (n=101) versus T2 (n=60), 58.72 [±11.38] versus 64.70 [±13.34]; *t*-test 3.02; p=0.003 • T0 (n=101) versus T3 (n=35), 58.72 [±11.38] versus 67.40 [±13.93]; *t*-test 3.66; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 with each other but not for the periods T1 to T2 and T2 to T3, for the immediately eligible adolescents: • T1 (n=101) versus T2 (n=60), 60.89 [±12.17] versus 64.70 [±13.34]; *t*-test 1.85; p=0.07 • T1 (n=101) versus T3 (n=35), 60.89 [±12.17] versus 67.40 [±13.93], *t*-test 2.63; p<0.001 • T2 (n=60) versus T3 (n=35), 64.70 [±13.34] versus 67.40 [±13.93], *t*-test 0.94; p=0.35 The immediately eligible adolescents had a CGAS score which was not	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			statistically significantly different compared to the sample of children/ adolescents without observed psychological /psychiatric symptoms after 12 months of puberty suppression (T3, *t*=0.01, *p*=0.99).	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
de Vries A, Steensma T, Doreleijers T, et al. (2011) Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. The Journal of Sexual Medicine 8 (8):2276-83. Netherlands Prospective longitudinal observational single centre before and after study.	The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Inclusion criteria were if they subsequently started gender-affirming hormones between 2003 and 2009 (mean [±SD] age at start of GnRH analogues was 14.75 [±1.92] years)[1]. No specific exclusion criteria were described. No diagnostic criteria or concomitant treatments were reported. Tanner stage of the included adolescents was not reported.	**Intervention** 70 adolescents were assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** The same 70 adolescents were assessed again at follow-up (T1), shortly before starting gender-affirming hormones. Not all adolescents completed all assessments for all items[2].	**Critical outcomes** ***Impact on gender dysphoria*** Impact on gender dysphoria was assessed using the Utrecht Gender Dysphoria Scale (UGDS). • There was no statistically significant difference in UGDS scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more gender dysphoria, *F* (*df, errdf*), *P*: 15.98 (1,39), p<0.001. ***Impact on mental health*** Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II). • There was a statistically significant reduction in BDI score between T0 and T1, n=41, 8.31 [±7.12] versus 4.95 [±6.72], *F* (*df, errdf*), *P*: 9.28 (1,39), p=0.004. • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females, *F* (*df, errdf*), *P*: 3.85 (1,39), p=0.057.	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. no non-exposed cohort 3. no description 4. no **Domain 2: Comparability** 1. study controls for age, age at start of treatment, IQ, and parental factors **Domain 3: Outcome** 1. no description 2. no/unclear 3. complete **Overall quality is assessed as poor**. Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This study was supported by a personal

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Anger and anxiety were assessed using Trait Anger and Anxiety (TPI and STAI, respectively) Scales of the State-Trait Personality Inventory. • There was no statistically significant difference in anger (TPI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anger compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.70 (1,39), p=0.022. • Similarly, there was no statistically significant difference in anxiety (STAI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anxiety compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 16.07 (1,39), p<0.001. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Impact on body image*** Impact on body image was assessed using the Body Image Scale to measure body satisfaction (BIS). There was no statistically significant difference between T0 and T1 for any of the 3 BIS scores (primary sex characteristics, secondary sex characteristics or neutral characteristics,	grant awarded to the first author by the Netherlands Organization for Health Research and Development.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			n=57). There were statistically significant differences between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more dissatisfaction, for: • primary sexual characteristics, *F* (*df, errdf*), *P*: 4.11 (1,55), p=0.047. • secondary sexual characteristics, *F* (*df, errdf*), *P*: 11.57 (1,55), p=0.001. But no statistically significant difference between sex assigned at birth males and sex assigned at birth females was found for neutral characteristics. However, there was a significant interaction effect between sex assigned at birth sex and the changes of gender dysphoria between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary sex characteristics compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 14.59 (1,55), p<0.001) and neutral characteristics, *F* (*df, errdf*), *P*: 15.26 (1,55), p<0.001). ***Psychosocial impact*** Psychosocial impact was assessed using both the Child Behaviour Checklist (CBCL) and the Youth Self-Report (YSR) to parents and adolescents, respectively. The Children's Global Assessment Scale was also reported. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] parental CBCL scores between T0 and T1[4] for all adolescents (n=54): • Total score (T0 – T1) 60.70 [±12.76] versus 54.46 [±11.23], *F* (*df, errdf*), *P*: 26.17 (1,52), p<0.001.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• Internalising score (T0 – T1) 61.00 [±12.21] versus 54.56 [±10.22], *F* (*df, errdf*), *P*: 22.93 (1,52), p<0.001. • Externalising score (T0 – T1) 58.04 [±12.99] versus 53.81 [±11.86], *F* (*df, errdf*), *P*: 12.04 (1,52), p=0.001. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising CBCL score but there was a significant difference for the externalising score: • Externalising score, *F* (*df, errdf*), *P*: 6.29 (1,52), p=0.015. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] YSR scores between T0 and T1 for all adolescents (n=54): • Total score (T0 – T1) 55.46 [±11.56] versus 50.00 [±10.56], *F* (*df, errdf*), *P*: 16.24 (1,52), p<0.001. • Internalising score (T0 – T1) 56.04 [±12.49] versus 49.78 [±11.63], *F* (*df, errdf*), *P*: 15.05 (1,52), p<0.001. • Externalising score (T0 – T1) 53.30 [±11.87] versus 49.98 [±9.35], *F* (*df, errdf*), *P*: 7.26 (1,52), p=0.009. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising YSR score but there was a significant difference for the externalising score: • Externalising score, *F* (*df, errdf*), *P*: 9.14 (1,52), p=0.004. There was a statistically significant increase in CGAS mean (±SD) score between T0 and T1 (n=41), 70.24 [±10.12] versus 73.90 [±9.63], *F* (*df, errdf*), *P*: 8.76	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			(1,39), p=0.005. There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting lower score for global functioning compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.77 (1,52), p=0.021. The proportion of adolescents scoring in the clinical range significantly decreased between T0 and T1, on the CBCL total problem scale (44.4% versus 22.2%, X^2[1] = 6.00, p=0.001), and the internalising scale (29.6% versus 11.1%, X^2[1] = 5.71, p=0.017) of the YSR.	

[1] There were statistically significant mean age [±SD] differences between sex assigned at birth males and sex assigned at birth females for age at assessment (13.14 [±1.55] versus 14.10 [±1.99] years, p=0.028), age at start of GnRH analogues (14.25 [±1.79] versus 15.21 [±1.95] years, p=0.036) and age at the start of gender-affirming hormones (16.24 [±1.21] versus 16.99 [±1.09] years, p=0.008). No statistically significant differences were seen for other baseline characteristics, time between GnRH analogue and gender-affirming hormones, full scale IQ, parental marital status, education, and sexual attraction to own, other or both sexes.
[2] Independent t-tests between mean scores on the CBCL, YSR, BDI, TPI, STAI, CGAS, UGS, and BIS of adolescents who completed both assessments and mean scores of adolescents who completed only one of the assessments revealed no significant differences on all used measures, at neither T0 or at T1.
[3] The CBCL/YSR has 2 components: Internalising score which sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores; externalising score which sums rule-breaking and aggressive behaviour. The total problems score is the sum of the scores of all the problem items. The YSR is a child self-report version of the CBCL.
[4] A repeated measures ANOVA (analysis of variance) was used.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Joseph T, Ting J, Butler G. (2019) The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. Journal of pediatric endocrinology & metabolism 32(10): 1077-1081 United Kingdom	Adolescents (12 to 14 years) with gender dysphoria (no diagnostic criteria described), n=70, including 31 transfemales and 39 transmales. All had been seen and assessed by a Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. All participants had entered puberty	Treatment with a GnRH analogue for at least 1 year or ongoing until they reached 16 years. No specific treatment, dose or route of administration reported. No concomitant treatments were reported.	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar*[1]** **Lumbar spine bone mineral apparent density (BMAD)[2] 0 to 1 year** Transfemales (mean [±SD]): 0.235 (0.030) g/cm3 at baseline, 0.233 g/cm3 (0.029) at 1 year (p=0.459); z-score 0.859 (0.154) at baseline, −0.228 (1.027) at 1 year (p=0.000) Transmales (mean [±SD]):	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Retrospective longitudinal observational single centre study To investigate whether there is any significant loss of bone mineral density (BMD) and bone mineral apparent density (BMAD) for up to 3 years of GnRH analogues. To investigate whether there was a significant drop after 1 year of treatment following abrupt withdrawal. 2011 to 2016	and all but 2 of the transmales were postmenarchal. 57% of the transfemales were in early puberty (G2–3 and testicular volume >4 mL) and 43% were in late puberty (G4–5). Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported.	No comparator.	0.196 (0.035) g/cm3 at baseline, 0.201 (0.033) g/cm3 at 1 year (p=0.074); z-score −0.186 (1.230) at baseline, −0.541 (1.396) at 1 year (p=0.006) **Lumbar spine BMAD 0 to 2 years** Transfemales (mean [±SD]): 0.240 (0.027) g/cm3 at baseline, 0.240 (0.030) g/cm3 at 2 years (p=0.865); z-score 0.486 (0.809) at baseline, −0.279 (0.930) at 2 years (p=0.000) Transmales (mean [±SD]): 0.195 (0.058) g/cm3 at baseline, 0.198 (0.055) at 2 years (p=0.433); z-score −0.361 (1.439) at baseline, −0.913 (1.318) at 2 years (p=0.001) **Lumbar spine bone mineral density (BMD) 0 to 1 year** Transfemales (mean [±SD]): 0.860 (0.154) kg/m2 at baseline, 0.859 (0.129) kg/m2 at 1 year (p=0.962); z-score −0.016 (1.106) at baseline, −0.461 (1.121) at 1 year (p=0.003) Transmales (mean [±SD]): 0.694 (0.149) kg/m2 at baseline, 0.718 (0.124) kg/m2 at 1 year (p=0.006); z-score −0.395 (1.428) at baseline, −1.276 (1.410) at 1 year (p=0.000) **Lumbar spine BMD 0 to 2 years** Transfemales (mean [±SD]): 0.867 (0.141) kg/m2 at baseline, 0.878 (0.130) kg/m2 at 2 years (p=0.395); z-score 0.130 (0.972) at baseline, −0.890 (1.075) at 2 years (p=0.000) Transmales (mean [±SD]): 0.695 (0.220) kg/m2 at baseline, 0.731 (0.209) kg/m2 at 2 years (p=0.058); z-score −0.715 (1.406) at baseline, −2.000 (1.384) at 2 years (p=0.000) ***Bone density: femoral***	**Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes 3. No statement **Overall quality is assessed as poor**. Other comments: although the evidence is of poor quality, the results suggest a possible association between GnRH analogues and BMAD. However, the results are not reliable and could be due to bias or chance. Further details of how the sample was drawn are not reported. No concomitant treatments were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Femoral neck (hip) BMD 0 to 1 year Transfemales (mean [±SD]): 0.894 (0.118) kg/m2 at baseline, 0.905 (0.104) kg/m2 at 1 year (p=0.571); z-score 0.157 (0.905) at baseline, −0.340 (0.816) at 1 year (p=0.002) Transmales (mean [±SD]): 0.772 (0.137) kg/m2 at baseline, 0.785 (0.120) kg/m2 at 1 year (p=0.797); z-score −0.863 (1.215) at baseline, −1.440 (1.075) at 1 year (p=0.000) **Femoral neck (hip) BMD 0 to 2 years** Transfemales (mean [±SD]): 0.920 (0.116) kg/m2 at baseline, 0.910 (0.125) kg/m2 at 2 years (p=0.402); z-score 0.450 (0.781) at baseline, −0.600 (1.059) at 2 years (p=0.002) Transmales (mean [±SD]): 0.766 (0.215) kg/m2 at baseline, 0.773 (0.197) at 2 years (p=0.604); z-score −1.075 (1.145) at baseline, −1.779 (0.816) at 2 years (p=0.001)	

[1] Lumbar spine (L1-L4) BMD was measured by yearly dual energy X-ray absorptiometry (DXA) scans at baseline (n=70), 1 year (n=70), and 2 years (n=31).
[2] BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. Reported as g/cm3 and z-scores. Hip BMAD z-scores were not calculated as there were no available reference ranges.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Khatchadourian K, Shazhan A, Metzger D. (2014) Clinical management of youth with gender dysphoria in Vancouver. The Journal of Pediatrics 164 (4): 906-11. Canada Retrospective observational chart review single centre study	27 young people with gender dysphoria who started GnRH analogues (at mean age [±SD] 14.7±1.9 years) out of 84 young people seen at the unit between 1998 and 2011. Note: the transmale and transfemale subgroups reported in the paper is discrepant, 15 transmales and 11 transfemales (n=26) reported in the outcomes section rather than the n=27	**Intervention** 84 young people with gender dysphoria were included. For GnRH analogues no specific treatment, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Stopping treatment*** The authors report that of 15 transmales taking GnRH analogues: • 14 transitioned to testosterone treatment during the observation period • 7 continued taking GnRH analogues after starting testosterone	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. not reported 2. no non-exposed cohort 3. secure record 4. no **Domain 2: Comparability** 1. not applicable **Domain 3: Outcome**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	stated in the paper; complete outcome reporting is also incomplete for the transfemale group. Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.		• 7 discontinued GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: ○ 5 discontinued after hysterectomy and salpingo-oophorectomy ○ 1 discontinued after 2.2 years (transitioned to gender-affirming hormone) ○ 1 discontinued after <2 months due to mood and emotional lability The authors report that of 11 transfemales taking GnRH analogues: • 5 received oestrogen treatment during the observation period • 4 continued taking GnRH analogues during oestrogen treatment • 1 discontinued GnRH analogues during oestrogen treatment (no reason reported) • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before oestrogen treatment (the following year delayed due to heavy smoking) • 1 discontinued GnRH analogues after 13 months due to choosing not to pursue transition ***Safety*** Of the 27 patients treated with GnRH analogues: • 1 transmale participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale participant developed leg pains and headaches on GnRH analogues, which eventually resolved without treatment.	1. record linkage 2. yes 3. in complete missing data **Overall quality is assessed as poor.** Other comments: mental health comorbidity was reported for all participants but not for the GnRH analogue cohort separately. Concomitant use of other medicines was not reported. Source of funding: No source of funding identified.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• 1 participant gained 19 kg within 9 months of initiating GnRH analogues, although their body mass index was >85 percentile before GnRH analogues.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of clinical endocrinology and metabolism 100(2): e270-5 Netherlands Retrospective longitudinal observational single centre study To assess BMD development during GnRH analogues and at age 22 years in adolescents with gender dysphoria who started treatment for gender dysphoria during adolescence. 1998 to 2012	34 adolescents (mean age ±SD 14.9±1.9 for transfemales and 15.0±2.0 for transmales at start of GnRH analogues). Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	The intervention was GnRH analogue monotherapy (triptorelin pamoate 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones from 16 years with discontinuation of GnRH analogue after gonadectomy. Median duration of GnRH analogue monotherapy in transfemales was 1.3 years (range, 0.5 to 3.8 years), and in transmales was 1.5 years (range, 0.25 to 5.2 years).	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.22 (0.03) g/cm3, gender-affirming hormones: 0.22 (0.02) g/cm3 (NS); z-score GnRH analogue: −0.44 (1.10), gender-affirming hormones: −0.90 (0.80) (p=NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]: GnRH analogue: 0.25 (0.03) g/cm3, gender-affirming hormones: 0.24 (0.02) g/cm3 (NS); z-score GnRH analogue: 0.28 (0.90), gender-affirming hormones: −0.50 (0.81) (p=0.004) **Lumbar spine bone mineral density (BMD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group **Domain 3: Outcome** 1. via routine clinical records 2. yes 3. follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor**. Other comments: Within person comparison. Small numbers of participants in each subgroup. No concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.84 (0.13) g/m2, gender-affirming hormones: 0.84 (0.11) g/m2 (NS); z-score GnRH analogue: −0.77 (0.89), gender-affirming hormones: −1.01 (0.98) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]): GnRH analogue: 0.95 (0.12) g/m2, gender-affirming hormones: 0.91 (0.10) g/m2 (p=0.006); z-score GnRH analogue: 0.17 (1.18), gender-affirming hormones: −0.72 (0.99) (p<0.001) ***Bone density; femoral*** **Femoral area BMAD[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.28 (0.04) g/cm3, gender-affirming hormones: 0.26 (0.04) g/cm3 (NS); z-score GnRH analogue: −0.93 (1.22), gender-affirming hormones: −1.57 (1.74) (p=NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.32 (0.04) g/cm3, gender-affirming hormones: 0.31 (0.04) (NS); z-score GnRH analogue: 0.01 (0.70), gender-affirming hormones: −0.28 (0.74) (NS)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Femoral area BMD[1] Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.88 (0.12) g/m2, gender-affirming hormones: 0.87 (0.08) (NS); z-score GnRH analogue: −0.66 (0.77), gender-affirming hormones: −0.95 (0.63) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.92 (0.10) g/m2, gender-affirming hormones: 0.88 (0.09) (p=0.005); z-score GnRH analogue: 0.36 (0.88), gender-affirming hormones: −0.35 (0.79) (p=0.001)	

[1] BMD and BMAD of the lumbar spine and femoral region (nondominant side) measured by DXA scans at start of GnRH analogues, (n=32), start of gender-affirming hormones (n=34), and at 22 years (n=34).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA et al. (2016) Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. The journal of sexual medicine 13(7): 1125-32	Adolescents with gender dysphoria (n=116), median age (range) 13.6 years (11.6 to 17.9) in transfemales and 14.2 years (11.1 to 18.6) in transmales during first year of GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were	GnRH analogue monotherapy (triptorelin pamoate 3.75 mg at 0, 2 and 4 weeks followed by injections every 4 weeks, route of administration not described) for at least 3 months.	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Other safety outcomes: liver function*** Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Netherlands Prospective longitudinal study To describe the changes in Tanner stage, testicular volume, gonadotropins, and sex steroids during GnRH analogues of adolescents with gender dysphoria to evaluate the efficacy. To report on liver enzymes, renal function and changes in body composition. 1998 to 2009	reported.		levels did not significantly change from baseline to 12 months of treatment. No values or statistical analyses were reported. ***Other safety outcomes: kidney function*** **Change in serum creatinine between 0 and 1 year** Transfemales (mean [±SD]): 70 (12) micromol/l at baseline, 66 (13) micromol/l at 1 year (p=0.20) Transmales (mean [±SD]): 73 (8) micromol/l at baseline, 68 (13) micromol/l at 1 year (p=0.01)	**Domain 3: Outcome** 1. via routine clinical records 2. yes 3. no statement **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments or comorbidities were reported. Source of funding: Ferring pharmaceuticals (triptorelin manufacturer)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Staphorsius A, Baudewijntje P, Kreukels P, et al. (2015) Puberty suppression and executive functioning: an fMRI-study in adolescents with gender dysphoria. Psychoneuroendocrinology 565:190-9. Netherlands Cross-sectional (single time point) assessment single centre study	The inclusion criteria were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. For all group's exclusion criteria were an insufficient command of the Dutch language (how assessed not reported), unadjusted endocrine disorders, neurological or psychiatric disorders that could lead to deviant test results (details not reported) use	**Intervention** GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously or intramuscularly). **Comparison** The comparison was between adolescents with gender dysphoria receiving GnRH analogues and those without GnRH	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact*** The Child Behaviour Checklist (CBCL) was used to assess psychosocial impact. The CBCL was administered once during the study. The reported outcomes for each group were (n, mean [±SD]): • Transfemales (all, n=18) 57.8 [±9.2] • Transfemales on GnRH analogues (n=8) 57.4 [±9.8] • Transfemales without GnRH analogues (n=10) 58.2 [±9.3]	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. somewhat representative of children and adolescents who have gender dysphoria 2. drawn from the same community as the exposed cohort 3. via routine clinical records 4. no **Domain 2: Comparability** 1. study controls for age and diagnosis

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	of psychotropic medication, and contraindications for an MRI scan. Additionally, adolescents receiving puberty delaying medication or any form of hormones besides oral contraceptives were excluded as controls. The sample size was 85 of whom 41 were adolescents (the numbers are discrepant with the number for whom outcomes are reported n=40) with gender dysphoria (20 of whom were being treated with GnRH analogues); 24 girls and 21 boys without gender dysphoria acted as controls (not further reported here). Details of the sampling frame are not reported. The ages at which GnRH analogues were started was not reported. The mean duration of treatment was 1.6 years (SD 1.0) Mean (±SD) Tanner stage for each group was reported: • Transfemales 3.9 [±1.1] • Transfemales on GnRH analogues 4.1 [±1.0] • Transfemales without GnRH analogues 3.8 [±1.1] • Transmales 4.5 [±0.9] • Transmales on GnRH analogues 4.1 [±1.1] Transmales without GnRH analogues 4.9 [±0.3]	analogues.	• Transmales (all, n=22) 60.4 [±10.2] • Transmales on GnRH analogues (n=12) 57.5 [±9.4] • Transmales without GnRH analogues (n=10) 63.9 [±10.5] The analysis of the CBCL data is not discussed, and statistical analysis is unclear. ***Cognitive development or functioning*** **IQ**[1] • Transfemales (mean [±SD]) on GnRH analogues: 94.0 (10.3) • Transfemales (mean [±SD]) without GnRH analogues: 109.4 (21.2) • Transmales (mean [±SD]) on GnRH analogues: 95.8 (15.6) • Transmales (mean [±SD]) without GnRH analogues: 98.5 (15.9) **Reaction time**[2] • Transfemales (mean [±SD]) on GnRH analogues: 10.9 (4.1) • Transfemales (mean [±SD]) without GnRH analogues: 9.9 (3.1) • Transmales (mean [±SD]) on GnRH analogues: 9.9 (3.1) • Transmales (mean [±SD]) without GnRH analogues: 10.0 (2.0) **Accuracy**[3] • Transfemales (mean [±SD]) on GnRH analogues: 73.9 (9.1) • Transfemales (mean [±SD]) without GnRH analogues: 83.4 (9.5) • Transmales (mean [±SD]) on GnRH analogues: 85.7 (10.5) • Transmales (mean [±SD]) without	**Domain 3: Outcome** 1. via clinical assessment 2. yes 3. unclear **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This work was supported by an educational grant from the pharmaceutical firm Ferring BV, and by a VICI grant (453-08-003) from the Dutch Science Foundation. The authors state that funding sources did not play a role in any component of this study.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			GnRH analogues: 88.8 (9.7)	

[1] Estimated with 4 subscales (arithmetic, vocabulary, picture arrangement, and block design) of the Wechsler Intelligence Scale for Children, third edition (WISC-III®, Wechsler 1991) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III®, Wechsler 1997), depending on the participant's age.
[2] Reaction time in seconds in the Tower of London task
[3] Percentage of correct trials in the Tower of London task

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Vlot, Mariska C, Klink, Daniel T, den Heijer, Martin et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 Netherlands Retrospective observational data analysis study To investigate the course of 3 bone turnover markers in relation to bonemineral density, in adolescents with gender dysphoria during GnRH analogue and gender-affirming hormones. 2001 to 2011	Adolescents with gender dysphoria, n=70. Median age (range) 15.1 years (11.7 to 18.6) for transmales and 13.5 years (11.5 to 18.3) for transfemales at start of GnRH analogues. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were treated with GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales group had a bone age of <15 years and the old transfemales group ≥15 years.	GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously).	**Critical outcomes** No critical outcomes reported **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.21 (0.17 to 0.25) g/cm3, gender-affirming hormones: 0.20 (0.18 to 0.24) g/cm3 (NS); z-score GnRH analogue: −0.20 (−1.82 to 1.18), gender-affirming hormones: −1.52 (−2.36 to 0.42) (p=0.001) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.22 (0.18 to 0.25) g/cm3, gender-affirming hormones: 0.22 (0.19 to 0.24) g/cm3 (NS); z-score GnRH analogue: −1.18 (−1.78 to 1.09), gender-affirming hormones: −1.15 (−2.21 to 0.08) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.23 (0.20 to 0.29) g/cm3, gender-affirming	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No **Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes 3. Follow-up rate variable across outcomes and no description of those lost **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments were reported. Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			hormones: 0.23 (0.19 to 0.28) g/cm3 (NS); z-score GnRH analogue: −0.05 (−0.78 to 2.94), gender-affirming hormones: −0.84 (−2.20 to 0.87) (p=0.003) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.26 (0.21 to 0.29) g/cm3, gender-affirming hormones: 0.24 (0.20 to 0.28) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.60 to 1.80), gender-affirming hormones: −0.29 (−2.28 to 0.90) (p≤ 0.0001) ***Bone density; femoral*** **Femoral neck BMAD** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.29 (0.20 to 0.33) g/cm3, gender-affirming hormones: 0.27 (0.20 to 0.33) g/cm3 (p≤0.1); z-score GnRH analogue: −0.71 (−3.35 to 0.37), gender-affirming hormones: −1.32 (−3.39 to 0.21) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.30 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.26 to 0.34) g/cm3 (NS); z-score GnRH analogue: −0.44 (−1.37 to 0.93), gender-affirming hormones: −0.36 (−1.50 to 0.46) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]),	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			GnRH analogue: 0.31 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.22 to 0.35) g/cm3 (NS); z-score GnRH analogue: −0.01 (−1.30 to 0.91), gender-affirming hormones: −0.37 (−2.28 to 0.47) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.33 (0.25 to 0.39) g/cm3, gender-affirming hormones: 0.30 (0.23 to 0.41) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.39 to 1.32), gender-affirming hormones: −0.27 (−1.91 to 1.29) (p=0.002)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa tool for cohort studies

Question	
Domain: Selection	
1. Representativeness of the exposed cohort	Truly representative of the average [describe] in the community Somewhat representative of the average [describe] in the community Selected group of users e.g. nurses, volunteers No description of the derivation of the cohort
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort Drawn from a different source No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	Secure record (e.g. surgical records) Structured interview Written self-report No description
4. Demonstration that outcome of interest was not present at start of study	Yes / No
Domain: Comparability	
1. Comparability of cohorts on the basis of the design or analysis	Study controls for [select most important factor] Study controls for any additional factor [this criteria could be modified to indicate specific control for a second important factor]
Domain: Outcome	
1. Assessment of outcome	Independent blind assessment Record linkage Self-report No description
2. Was follow-up long enough for outcomes to occur	Yes [select and adequate follow up period for outcome of interest] No
3. Adequacy of follow up of cohorts	Complete follow up (all subjects accounted for) Subjects lost to follow up unlikely to introduce bias (small number lost to follow up [select an adequate %] follow up or description provided of those lost) Follow up rate [select an adequate %] and no description of those lost No statement

Appendix G Grade profiles

Table 2: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria									
Mean±SD Utrecht Gender Dysphoria Scale[1] (version(s) not reported), time point at baseline (before GnRH analogues) versus follow-up (before gender-affirming hormones, higher scores indicate more gender dysphoria)									
1 cohort study de Vries et al 2011	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 53.20±7.91 GnRH analogue: 53.9±17.42 *P*=0.333	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.
2 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 3: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Beck Depression Inventory-II, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones). (Lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 8.31±7.12 GnRH analogue: 4.95±6.72 *P*=0.004	Critical	VERY LOW
Mean±SD Trait Anger (TPI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 18.29±5.54 GnRH analogue: 17.88±5.24 *P*=0.503	Critical	VERY LOW
Mean±SD Trait Anxiety (STAI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 39.43±10.07 GnRH analogue: 37.95±9.38 *P*=0.276	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 4: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – body image

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image									
Mean±SD Body Image Scale (primary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 4.10±0.56 GnRH analogue: 3.98±0.71 *P*=0.145	Important	VERY LOW
Mean±SD Body Image Scale (secondary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.74±0.65 GnRH analogue: 2.82±0.68 *P*=0.569	Important	VERY LOW
Mean±SD Body Image Scale (neutral characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.41±0.63 GnRH analogue: 2.47±0.56 *P*=0.620	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 5: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – psychosocial impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline, higher scores indicate benefit)									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 58.72 [±11.38]	n=100 56.63 [±13.14]	*P*=0.23	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 6 months[2] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 60.89 [±12.17]	n=100 60.29 [±12.81]	*P*=0.73	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 12 months[3] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=60 64.70 [±13.34]	n=61 62.97 [±14.10]	*P*=0.49	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 18 months[4] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=35 67.40 [±13.93]	n=36 62.53 [±13.54]	*P*=0.14	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 6 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=101	None	Baseline: 58.72±11.38 6 months: 60.89±12.17 *P*=0.19	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	Baseline: 58.72±11.38 12 months: 64.70±13.34 *P*=0.003	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	Baseline: 58.72±11.38 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	6 months: 60.89±12.17 12 months: 64.70±13.34 *P*=0.07	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	6 months: 60.89±12.17 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=60 N=35	None	12 months: 64.70±13.34 18 months: 67.40±13.93 *P*=0.35	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 6 months[2] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=201	None	Baseline: 57.73±12.27 6 months: 60.68±12.47 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months[3] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	Baseline: 57.73±12.27 12 months: 63.31±14.41 *P*<0.001	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months[4] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	Baseline: 57.73±12.27 18 months: 64.93±13.85 *P*<0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	6 months: 60.68±12.47 12 months: 63.31±14.41 *P*<0.08	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	6 months: 60.68±12.47 18 months: 64.93±13.85 *P*<0.02	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=121 N=71	None	12 months: 63.31±14.41 18 months: 64.93±13.85 *P*<0.45	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, higher scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 70.24±10.12 GnRH analogue: 73.90±9.63 *P*=0.005	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Child Behaviour Checklist (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 60.70±12.76 GnRH analogue: 54.46±11.23 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 61.00±12.21 GnRH analogue: 52.1±9.81 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 58.04±12.99 GnRH analogue: 53.81±11.86 *P*=0.001	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Child Behaviour Checklist total problem scale, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 44.4% GnRH analogue: 22,2% *P*=0.001	Important	VERY LOW
Mean±SD Youth Self-Report (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormone, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 55.46±11.56 GnRH analogue: 50.00±10.56 *P*<0.001	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 56.04±12.49 GnRH analogue: 49.78±11.63 *P*<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 53.30±11.87 GnRH analogue: 49.98±9.35 *P*=0.009	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 29.6% GnRH analogue: 11.1% *P*=0.017	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transfemales (lower scores indicate benefit									
1 cross-sectional study Staphorsius et al 2015	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=8	N=10	GnRH analogue: 57.4 [±9.8] No GnRH analogue: 58.2 [±9.3]	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transmales (lower scores indicate benefit)									
1 cross-sectional study Staphorsius et al 2015	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=12	N=10	GnRH analogues: 57.5 [±9.4] No GnRH analogue: 63.9 [±10.5]	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 6 months from baseline (after 6 months of psychological support – both groups).
3 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
4 18 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
5 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
6 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 6: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – engagement with healthcare services

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Engagement with healthcare services									
Number (proportion) failing to engage with health care services (did not attend clinic), at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/214 (4.2%)	None	9 adolescents out of 214 failed to attend clinic and were excluded from the study (4.2%)	Important	VERY LOW
Loss to follow-up									
1 cohort study Costa et al 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	201	None	The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 7: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – stopping treatment

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Stopping treatment									
Number (proportion) stopping GnRH analogues, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/143 (6.2%)	None	9/143 adolescents stopped GnRH analogues (6.2%)[2]	Important	VERY LOW
Number (proportion) stopping from GnRH analogues, at (up to) 13 years follow-up									
1 cohort study Khatchadourian et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	11/27 (42%)	None	11/26 stopped GnRH analogues (42%)[4]	Important	VERY LOW
Number (proportion) stopping GnRH analogues but who wished to continue endocrine treatment, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	4/143 (2.8%)	None	4/143 adolescents stopped GnRH analogues but wished to continue treatment (2.8%)	Important	VERY LOW
Number (proportion) stopping GnRH analogues who no longer wished gender-affirming treatment, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	5/143 (3.5%)	None	5/143 adolescents stopped GnRH analogues and no longer wished to continue gender-affirming treatment (3.5%)	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), although they wanted to continue treatments for gender dysphoria, GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability).

3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

4 Because of transitioning to gender-affirming hormones or gender-affirming surgery, adverse effects (such as mood and emotional lability) or no longer wishing to pursue transition.

Table 8. Question 2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Bone density: change in lumbar BMAD									
Change in lumbar spine BMAD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), g/cm^3 Baseline: 0.235 (0.030) 1 year: 0.233 (0.029) p=0.459 z-score Baseline: 0.859 (0.154) 1 year: −0.228 (1.027) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), g/cm^3 Baseline: 0.196 (0.035) 1 year: 0.201 (0.033) p=0.074 z-score Baseline: −0.186 (1.230) 1 year: −0.541 (1.396) p=0.006	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar spine BMAD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), g/cm^3 Baseline: 0.240 (0.027) 2 years: 0.240 (0.030) p=0.865 z-score Baseline: 0.486 (0.809) 2 years: −0.279 (0.930) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), g/cm^3 Baseline: 0.195 (0.058) 2 years: 0.198 (0.055) p=0.433 z-score Baseline: −0.361 (1.439) 2 years: −0.913 (1.318) p=0.001	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=11 N=12	None	Mean (SD), g/cm^3 GnRH analogue: 0.22 (0.03) Gender-affirming hormones: 0.22 (0.02) NS z-score GnRH analogue: −0.44 (1.10) Gender-affirming hormones: −0.90 (0.80) p-value: NS	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/cm^3 GnRH analogue: 0.25 (0.03) Gender-affirming hormones: 0.24 (0.02) NS z-score GnRH analogue: 0.28 (0.90) Gender-affirming hormones: −0.50 (0.81) p-value: 0.004	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/cm^3 GnRH analogue: 0.21 (0.17 to 0.25) Gender-affirming hormones: 0.20 (0.18 to 0.24) NS z-score GnRH analogue: −0.20 (−1.82 to 1.18) Gender-affirming hormones: −1.52 (−2.36 to 0.42) p-value: <0.01	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/cm^3 GnRH analogue: 0.22 (0.18 to 0.25) Gender-affirming hormones: 0.22 (0.19 to 0.24) NS z-score GnRH analogue: −1.18 (−1.78 to 1.09)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							Gender-affirming hormones: −1.15 (−2.21 to 0.08) p-value: p≤0.1		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/cm^3 GnRH analogue: 0.23 (0.20 to 0.29) Gender-affirming hormones: 0.23 (0.19 to 0.28) NS z-score GnRH analogue: −0.05 (−0.78 to 2.94) Gender-affirming hormones: −0.84 (−2.20 to 0.87) p-value: ≤0.01	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.26 (0.21 to 0.29) Gender-affirming hormones: 0.24 (0.20 to 0.28) p≤0.01 z-score GnRH analogue: 0.27 (−1.60 to 1.80) Gender-affirming hormones: −0.29 (−2.28 to 0.90) p-value: p ≤ 0.01)	IMPORTANT	VERY LOW
Bone density: change in lumbar BMD									
Change in lumbar spine BMD from baseline to 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.860 (0.154) 1 year: 0.859 (0.129) p=0.962 z-score Baseline: −0.016 (1.106) 1 year: −0.461 (1.121) p=0.003	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.694 (0.149) 1 year: 0.718 (0.124) p=0.006 z-score Baseline: −0.395 (1.428) 1 year: −1.276 (1.410) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.867 (0.141) 2 years: 0.878 (0.130) p=0.395 z-score Baseline: 0.130 (0.972) 2 years: −0.890 (1.075) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transmales									
1 observational study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.695 (0.220) 2 years: 0.731 (0.209) p=0.058	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: −0.715 (1.406) 2 years: −2.000 (1.384) p=0.000		
Change in lumbar BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=11	None	Mean (SD), g/m2 GnRH analogue: 0.84 (0.13) Gender-affirming hormones: 0.84 (0.11) NS z-score GnRH analogue: −0.77 (0.89) Gender-affirming hormones: −1.01 (0.98) NS	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/m2 GnRH analogue: 0.95 (0.12) Gender-affirming hormones: 0.91 (0.10) p-value: 0.006 z-score GnRH analogue: 0.17 (1.18) Gender-affirming hormones: −0.72 (0.99) p-value: <0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMD									
Change in femoral neck BMD from baseline to 1 year in transfemales									
1 observational study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.894 (0.118) 1 year: 0.905 (0.104) p=0.571	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: 0.157 (0.905) 1 year: −0.340 (0.816) p=0.002		
Change from baseline to 1 year in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.772 (0.137) 1 year: 0.785 (0.120) p=0.797 z-score Baseline: −0.863 (1.215) 1 year: −1.440 (1.075) p=0.000	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.920 (0.116) 2 years: 0.910 (0.125) p=0.402 z-score Baseline: 0.450 (0.781) 2 years: −0.600 (1.059) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.766 (0.215) 2 years: 0.773 (0.197) p=0.604 z-score Baseline: −1.075 (1.145) 2 years: −1.779 (0.816) p=0.001	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Bone density: change in femoral neck (hip) BMAD									
Change from starting GnRH analogue to starting gender-affirming hormones in femoral neck BMAD in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/cm3 GnRH analogue: 0.29 (0.20 to 0.33) Gender-affirming hormones: 0.27 (0.20 to 0.33) p≤0.1 z-score GnRH analogue: −0.71 (−3.35 to 0.37) Gender-affirming hormones: −1.32 (−3.39 to 0.21) p≤0.1	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/cm3 GnRH analogue: 0.30 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.26 to 0.34) NS z-score GnRH analogue: −0.44 (−1.37 to 0.93) Gender-affirming hormones: −0.36 (−1.50 to 0.46) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/cm3 GnRH analogue: 0.31 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.22 to 0.35)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Vlot et al. 2017							NS z-score GnRH analogue: −0.01 (−1.30 to 0.91) Gender-affirming hormones: −0.37 (−2.28 to 0.47) NS		
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.33 (0.25 to 0.39) Gender-affirming hormones: 0.30 (0.23 to 0.41) p-value: ≤0.01 z-score GnRH analogue: 0.27 (−1.39 to 1.32) Gender-affirming hormones: −0.27 (−1.91 to 1.29) p-value: ≤0.01	IMPORTANT	VERY LOW
Bone density: change in femoral area BMD									
Change in femoral BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=14 N=6	None	Mean (SD), g/m2 GnRH analogue: 0.88 (0.12) Gender-affirming hormones: 0.87 (0.08) NS z-score GnRH analogue: −0.66 (0.77) Gender-affirming hormones: −0.95 (0.63) NS	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in femoral BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=13	None	Mean (SD), g/m2 GnRH analogue: 0.92 (0.10) Gender-affirming hormones: 0.88 (0.09) p-value: 0.005 z-score GnRH analogue: 0.36 (0.88) Gender-affirming hormones: −0.35 (0.79) p-value: 0.001	IMPORTANT	VERY LOW
Bone density: change in femoral area BMAD									
Change in femoral BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=10	None	Mean (SD), g/cm3 GnRH analogue: 0.28 (0.04) Gender-affirming hormones: 0.26 (0.04) NS z-score GnRH analogue: −0.93 (1.22) Gender-affirming hormones: −1.57 (1.74) p-value: NS	IMPORTANT	VERY LOW
Change in femoral BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=18	None	Mean (SD), g/cm3 GnRH analogue: 0.32 (0.04) Gender-affirming hormones: 0.31 (0.04) NS z-score	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							GnRH analogue: 0.01 (0.70) Gender-affirming hormones: −0.28 (0.74) NS		

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; NS, not significant; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Joseph et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no randomisation, no control group and high number of participants lost to follow-up).
3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

Table 9 Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – cognitive development or functioning

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Cognitive development or functioning (1 cross-sectional study)									
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 94.0 (10.3)	N=10 Mean (SD) 109.4 (21.2)	NR	IMPORTANT	VERY LOW
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 95.8 (15.6)	N=10 Mean (SD) 98.5 (15.9)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 10.9 (4.1)	N=10 Mean (SD) 9.9 (3.1)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 9.9 (3.1)	N=10 Mean (SD) 10.0 (2.0)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transfemales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 73.9 (9.1)	N=10 Mean (SD) 83.4 (9.5)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transmales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 85.7 (10.5)	N=10 Mean (SD) 88.8 (9.7)	NR	IMPORTANT	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 10: Question 2: In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Other safety outcomes: change in serum creatinine									
Change in serum creatinine (micromol/l) between baseline and 1 year in transfemales									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=28	None	Mean (SD) Baseline: 70 (12) 1 year: 66 (13) p-value: 0.20	IMPORTANT	VERY LOW
Change in serum creatinine (µmol/l) between baseline and 1 year in transmales									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=29	None	Mean (SD) Baseline: 73 (8) 1 year: 68 (13) p-value: 0.01	IMPORTANT	VERY LOW
Other safety outcomes: liver enzymes									
Presence of elevated liver enzymes (AST, ALT, and glutamyl transferase) between baseline and during treatment									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	39	None	Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during treatment than at baseline.	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							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									
1 cohort study Khatchadourian et al 2014	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable[2]	27	None	3/27 adolescents[3]	Important	VERY LOW

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GnRH, gonadotrophin releasing hormone; P, P-value; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Schagen et al. (2016) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

2 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

3 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. 1 transmale developed leg pains and headaches, which eventually resolved without treatment. 1 participant gained 19 kg within 9 months of initiating GnRH analogues.

Table 11: Question 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – critical outcomes

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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Impact on gender dysphoria									
Mean [±SD] Utrecht Gender Dysphoria Scale (version(s) not reported), time point at baseline (before GnRHa) versus follow-up (just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 47.95 [±9.70] score at T1 49.67 [±9.47]	n-NR[2] score at T0 56.57 [±3.89] score at T1 56.62 [±4.0]	*F*-ratio 15.98 (*df, errdf*: 1,39), *P*<0.001	Critical	VERY LOW
Impact on mental health									
Mean [±SD] Beck Depression Inventory-II, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 5.71 [±4.31] score at T1 3.50 [±4.58]	n-NR[2] score at T0 10.34 [±8.24] score at T1 6.09 [±7.93]	*F*-ratio 3.85 (*df, errdf*: 1,39), *P*=0.057	Critical	VERY LOW
Mean [±SD] Trait Anger (TPI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 5.22 [±2.76] score at T1 5.00 [±3.07]	n-NR[2] score at T0 6.43 [±2.78] score at T1 6.39 [±2.59]	*F*-ratio 5.70 (*df, errdf*: 1,39), *P*=0.022	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Mean [±SD] Trait Anxiety (STAI), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 4.33 [±2.68] score at T1 4.39 [±2.64]	n-NR[2] score at T0 7.00 [±2.36] score at T1 6.17 [±2.69]	*F*-ratio 16.07 (*df, errdf*: 1,39), *P*<0.001	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 The overall sample size completing the outcome at both time points was 41.

Table 11: Question: 4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria? – important outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Subgroups: sex assigned at birth males compared with sex assigned at birth females									
Impact on body image									
Mean [±SD] Body Image Scale (primary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 4.02 [±0.16] score at T1 3.74 [±0.78]	n-NR[2] score at T0 4.16 [±0.52] score at T1 4.17 [±0.58]	*F*-ratio 4.11 (*df, errdf*: 1,55), *P*=0.047	Important	VERY LOW
Mean [±SD] Body Image Scale (secondary sexual characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 2.66 [±0.50] score at T1 2.39 [±0.69]	n-NR[2] score at T0 2.81 [±0.76] score at T1 3.18 [±0.42]	*F*-ratio 11.57 (*df, errdf*: 1,55), *P*=0.001[3]	Important	VERY LOW
Mean [±SD] Body Image Scale (neutral characteristics), time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[2] score at T0 2.60 [±0.58] score at T1 2.32 [±0.59]	n-NR[2] score at T0 2.24 [±0.62] score at T1 2.61 [±0.50]	*F*-ratio 0.081 (*df, errdf*: 1,55), *P*=0.777[3]	Important	VERY LOW
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline.									
1 cohort study Costa et al 2015	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	n=not reported	n=not reported	*t*-test 2.15; *P*=0.03[5]	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	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).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[6] score at T0 73.10 [±8.84] score at T1 77.33 [±8.69]	n-NR[6] score at T0 67.25 [±11.06] score at T1 70.30 [±9.44]	*F*-ratio 5.77 (*df, errdf*: 1,39), *P*=0.021	Important	VERY LOW
Mean [±SD] Child Behaviour Checklist (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 59.42 [±11.78] score at T1 50.38 [±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).									
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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
Mean [±SD] Child Behaviour Checklist (externalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 54.71 [±12.91] score at T1 48.75 [±10.22]	n-NR[7] score at T0 60.70 [±12.64] score at T1 57.87 [±11.66]	*F*-ratio 6.29 (*df, errdf*: 1,52), *P*=0.015	Important	VERY LOW
Mean [±SD] Youth Self-Report (total T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 53.56 [±12.26] score at T1 47.84 [±10.86]	n-NR[7] score at T0 57.10 [±10.87] score at T1 51.86 [±10.11]	*F*-ratio 1.99 (*df, errdf*: 1,52), *P*=0.164	Important	VERY LOW
Mean [±SD] Youth Self-Report (internalising T) score, time point at baseline (T0 before GnRH analogues) versus follow-up (T1 just before gender-affirming hormones).									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 55.88 [±11.81] score at T1 49.24 [±12.24]	n-NR[7] score at T0 56.17 [±13.25] score at T1 50.24 [±11.28]	*F*-ratio 0.049 (*df, errdf*: 1,52), *P*=0.825	Important	VERY LOW
Mean [±SD] Youth Self-Report (externalising T) score, time point at baseline (T0 before GnRHa) versus follow-up (T1 just before gender-affirming hormones).									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Sex assigned at birth males	Sex assigned at birth females	Result		
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	n-NR[7] score at T0 48.72 [±11.83] score at T1 46.52 [±9.23]	n-NR[7] score at T0 57.24 [±10.59] score at T1 52.97 [±8.51]	*F*-ratio 9.14 (*df, errdf*: 1,52), *P*=0.004	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 The overall sample size completing the outcome at both time points was 57.
3 There was a significant interaction effect between sex assigned at birth and BDI between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary F (df, errdf), P: 14.59 (1,55), P<0.001) and neutral F (df, errdf), P: 15.26 (1,55), P<0.001) sex characteristics compared with sex assigned at birth males.
4 Serious limitations – the cohort study by Costa et al. 2015 was assessed as at high risk of bias (poor quality).
5 At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and females. There were no statistically significant differences in CGAS scores between gender dysphoric sex assigned at birth males and females in all follow-up evaluations (P>0.1; full data not reported).
6 The overall sample size completing the outcome at both time points was 41
7 The overall sample size completing the outcome at both time points was 54.

Glossary

Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating body size measurements using UK norms in growing adolescents.
Child Behaviour Checklist (CBCL)	CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents.
Children's Global Assessment Scale (CGAS)	The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning.
Gender	The roles, behaviours, activities, attributes, and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).
Gonadotrophin releasing hormone (GnRH) analogues	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of 2 gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in FSH and LH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Sex assigned at birth	Sex assigned at birth (male or female) is a biological term and is based on genes and how external and internal sex and reproductive organs work and respond to hormones. Sex is the label that is recorded when a baby's birth is registered.
Tanner stage	Tanner staging is a scale of physical development.
Trait Anger Spielberger scales of the State-Trait Personality Inventory (TPI)	The TPI is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transmale is a person who identifies as male and a transfemale is a person who identifies as female.

Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the impact on gender dysphoria.
Youth Self-Report (YSR)	The self-administered YSR is a checklist to detect emotional and behavioural problems in children and adolescents. It is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour.

References

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Evidence review: Gender-affirming hormones for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 21 October 2020. See summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

Contents

1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gender-affirming hormones for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see appendix A). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood (World Health Organisation 2020), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves[1] regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics (Diagnostic and Statistical Manual of Mental Disorders 2013).

Gender-affirming hormones are oestradiol for sex assigned at birth males (transfemales) and testosterone for sex assigned at birth females (transmales). The aim of gender-affirming hormones is to induce the development of the physical sex characteristics congruent with the individual's gender expression while aiming to improve mental health and quality of life outcomes.

No oestradiol-containing products are licensed for gender dysphoria and therefore any use for children and adolescents with gender dysphoria is off-label.

The only testosterone-containing product licensed for gender dysphoria is Sustanon 250 mg/ml solution for injection, which is indicated as supportive therapy for transmales, use of all other testosterone-containing products for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, to support young people and their families in managing the uncertainties inherent in gender identity development and to provide ongoing opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of gonadotrophin releasing hormone (GnRH) analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex (NHS England 2013).

Currently NHS England, as part of the Gender Identity Development Service for Children and Adolescents, routinely commissions gender-affirming hormones for young people with continuing gender dysphoria from around their 16th birthday subject to individuals meeting the eligibility and readiness criteria (Clinical Commissioning Policy 2016).

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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?

(c) what was the duration of treatment with GnRH analogues?

The most commonly reported diagnostic criteria for gender dysphoria was the DSM criteria in use at the time (5/10 studies). In 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017) DSM-IV-TR criteria was used. In 2 studies (Kuper et al. 2020 and Stoffers et al. 2019) DSM-V criteria was used. One study from Finland (Kaltiala et al. 2020) used the ICD-10 diagnosis of 'transexualism'. It was not reported how gender dysphoria was defined in the remaining 4 studies.

In the studies, treatment with gender-affirming hormones started at about 16 to 17 years, with a range of about 14 to 19 years. Most studies did not report the duration of treatment with GnRH analogues, but where this was reported there was a wide variation ranging from a few months up to about 5 years (Klaver et al. 2020, Klink et al. 2015 and Stoffers et al. 2019).

Discussion

The key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies.

All the studies included in the evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes seen were due to gender-affirming hormones or other treatments the participants may have received.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. Furthermore, participant numbers are poorly reported in some studies, with high numbers lost to follow-up or outcomes not reported for some participants. The authors provide no explanation for this incomplete reporting.

Details of the gender-affirming hormone treatment regimen are poorly reported in most of the included studies, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria.

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. In addition to this, most

outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine whether any statistically significant changes seen are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools (for example, by linking scores to symptom severity), so some conclusions can be made.

Conclusion

Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria.

Results from 5 uncontrolled, observational studies suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty using modified GRADE.

Safety outcomes were reported in 5 observational studies. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are required. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of patients who may benefit more from gender-affirming hormones.

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
   (c) what was the duration of GnRH analogues treatment?

See appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO and were conducted on 21 July 2020.

See appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See appendix C for evidence selection details and appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendix E and appendix F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See appendix G for GRADE Profiles.

4. Summary of included studies

Ten observational studies were included in the evidence review. Seven studies were retrospective observational studies (Allen et al. 2019, Kaltiala et al. 2020, Khatchadourian et al. 2014, Klaver et Al. 2020, Klink et al. 2015, Stoffers et al. 2019, Vlot et al. 2017) and three

studies were prospective longitudinal observational studies (Achille et al. 2020, Kuper et al. 2020, Lopez de Lara et al. 2020).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than saying natal or biological sex and 'cross sex hormones' are now referred to as 'gender-affirming hormones'. The research studies may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Achille et al. 2020 Prospective longitudinal study Single centre, New York, United States	50 children, adolescents and young adults with gender dysphoria; 17 transfemales and 33 transmales Mean age at baseline was 16.2 years (SD 2.2)	**Intervention** Endocrine interventions (the collective term used for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for Transgender Health (WPATH) guidelines Puberty suppression was: • GnRH analogue and/or anti-androgens (transfemales) • GnRH analogue or medroxyprogesterone (transmales) Once eligible, gender-affirming hormones were offered, these were: • Oestradiol (transfemales) • 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

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

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*

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

	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

Scale; HDL: high-density lipoproteins; LDL: low-density lipoproteins; p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire.

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with gender-affirming hormones?

(c) what was the duration of treatment with GnRH analogues?

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td>Diagnostic criteria</td><td>The DSM-IV-TR criteria was used in 3 studies (Klaver et al. 2020, Klink et al. 2015 and Vlot et al. 2017).

The DSM-V criteria was used in 2 studies (Kuper et al. 2020 and Stoffers et al. 2019). The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and think of themselves which must have lasted at least 6 months.

The ICD-10 diagnosis of ‘transsexualism’ was used in 1 study (Kaltiala et al. 2020). The authors state that this is the corresponding diagnosis to ‘gender dysphoria’ in the DSM-V, and that diagnostic assessments in the study location (Finland) take place according to ICD-10.

It was not reported how gender dysphoria was defined in the remaining 4 studies (VERY LOW).

From the evidence selected, the most commonly reported diagnostic criteria for gender dysphoria (5/10 studies) was the DSM criteria in use at the time the study was conducted.</td></tr>
<tr><td>Age when gender-affirming hormones started</td><td>8/10 studies reported the age at which participants started treatment with gender-affirming hormones, either as the mean age (with SD) or median age (with the range):

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

<table>
<tr><th>Study</th><th>Median age (range)</th></tr>
<tr><td>Stoffers et al. 2019</td><td>17.2 years (15 to 19.5)</td></tr>
<tr><td>Vlot et al. 2017</td><td>16.3 years (15.9 to 19.5) in transfemales
16.0 years (14.0 to 18.9) in transmales</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>Age at the start of treatment was not reported in 3 studies:
In Achille et al. 2020 the mean age at initial assessment (baseline) was 16.2 years (SD ±2.2)
In Kaltiala et al. 2020 the mean age at diagnosis was 18.1 years (range 15.2 to 19.9)
In Lopez de Lara et al. 2020 the mean age of participants was 16 years (range 14 to 18), although it is not clear if this is at the initial assessment or at the start of gender-affirming hormones.
The evidence included showed that most children and adolescents started treatment with gender-affirming hormones at about 16 to 17 years, with a range of about 14 to 19 years.</td></tr>
<tr><td>Duration of treatment with GnRH analogues</td><td>The duration of treatment with GnRH analogues was reported in 3/10 studies:<table><tr><th>Study</th><th>Median duration</th></tr><tr><td>Klaver et al. 2020</td><td>2.1 years (IQR 1.0 to 2.7) in transfemales
1.0 years (IQR 0.5 to 2.9) in transmales</td></tr><tr><td>Klink et al. 2015</td><td>1.3 years (range 0.5 to 3.8) in transfemales
1.5 years (range 0.25 to 5.2) in transmales
(GnRH analogue monotherapy)</td></tr><tr><td>Stoffers et al. 2019</td><td>8 months (range 3 to 39)</td></tr></table>The evidence included showed wide variation in the duration of treatment with gender-affirming hormones, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.</td></tr>
</table>

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; GnRH, Gonadotrophin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; IQR, interquartile range; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of gender-affirming hormones for children and adolescents with gender dysphoria is the lack of reliable comparative studies. All the studies included in this evidence review are uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using modified GRADE. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a 'no treatment arm' in comparative trials of gender-affirming hormones, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials. A fundamental limitation of all the uncontrolled studies included in this review is that any changes in scores from baseline to follow-up could be attributed to a regression-to-the-mean.

The included studies have relatively short follow-up, with an average duration of treatment with gender-affirming hormones between around 1 year and 5.8 years. Further studies with a

longer follow-up are needed to determine the long-term effect of gender-affirming hormones for children and adolescents with gender dysphoria.

Most studies included in this review did not report comorbidities (physical or mental health) and no study reported concomitant treatments in detail. Because of this it is not clear whether any changes observed were due to gender-affirming hormones or other treatments the participants may have received. For example, we do not know if any improvement in depression symptom score over time was the result of gender-affirming hormones or the mental health support the person may be receiving (including medicines or counselling). This may be of particular importance for the mental health outcomes discussed in this review, since depression, anxiety and other related symptoms are common in children and adolescents with gender dysphoria. In Achille et al. 2020, at baseline around one-third of participants were taking medicines for mental health problems and around two-thirds reported being depressed in the past year. In Kaltiala et al. 2020, half the participants needed mental health treatment during and before gender identity assessment, with the most common reasons for treatment being depression, anxiety and suicidality. Only 1 study reported outcomes adjusted for engagement in counselling and medicines for mental health problems (Achille et al. 2020). This study found that gender-affirming hormones had no significant impact on depression and quality of life when adjusted for mental health care, despite significant approvements reported for the unadjusted results. However, it is not possible to draw conclusions on the impact of concurrent mental health treatment on the effect of gender-affirming hormones based on this study alone. Details of the mental health care provided are not reported in the study and results are presented for transfemales and transmales separately, resulting in small patient numbers and possible underpowering.

In most of the included studies, details of the gender-affirming hormone treatment regimens are poorly reported, with limited information provided about the medicines, doses and routes of administration used. It is not clear whether the interventions used in the studies are reflective of current UK practice for children and adolescents with gender dysphoria. There is also the suggestion that the hormone dose used in 1 study may have been too low; the authors of Klink et al. 2015 suggest that the relatively low initial dose of oestrogen for transfemales may be the reason for the observed lack of effect on lumber spine bone density. Duration of treatment with a GnRH analogue is also poorly reported and is only stated in 3/10 studies.

There is a degree of indirectness in some studies, with some participants included that fall outside of the population of this evidence review. For example, in Kuper et al. 2020 17% of participants received puberty suppression alone, and in Achille et al. 2020, 30% of participants received no treatment or puberty suppression alone. Some results and statistical analyses are only reported for the whole cohort in these studies and not the subgroup of participants who received gender-affirming hormones.

Participant numbers are poorly reported in some of the included studies. In Achille et al. 2020, 47% (45/95) of the people who entered the study did not have follow-up data and were excluded from the analyses, with no explanation or description of those people lost to follow-up. In Kuper et al. 2020, the number of participants varied by outcome, with less than two-thirds of participants providing data for some outcomes. The authors provide no explanation for this incomplete reporting.

It is not clear whether some outcome measures, specifically those related to psychosocial functioning, are relevant to the UK population. In Kaltiala et al. 2020, an observational study conducted in Finland, the proportion of participants living with parents or guardians is reported as marker of appropriate functioning. The authors state that in Finnish culture young people tend to leave the parental home early, with only around one-quarter of 20 to 24 year olds still living at home. This is lower than in the UK, where around half of 20 to 24 year olds live with their parents or guardians (ONS: Why are more young people living with their parents?).

It is difficult to draw firm conclusions for many of the effectiveness and safety outcomes reported in the included studies because many different scoring tools and methods were used to assess the same outcome, often with conflicting results. For example, bone density is reported as bone mineral density (BMD) and bone mineral apparent density (BMAD) in the same study, the latter being a size-adjusted measure often useful for people whose bones are still growing. For some populations (transfemale versus transmale) and bone regions (lumber spine versus femoral neck), statistically significant differences in BMD are reported but not for BMAD, and vice versa.

In addition to this, most outcomes reported across the included studies do not have an accepted minimal clinically important difference (MCID), making it difficult the determine whether any observed statistically significant changes are clinically meaningful. However, the authors of some studies report thresholds to interpret the results of the scoring tools, so some conclusions can be made. For example, the mean Utrecht Gender Dysphoria Scale (UGDS) score (a measure of gender dysphoria symptoms) reduced to about 15 points after treatment with gender-affirming hormones (Lopez de Lara et al. 2020). The authors state that scores of 40 points or above signify gender dysphoria, suggesting that after about 12 months of treatment with gender-affirming hormones, the majority of participants did not have symptoms of gender dysphoria.

The impact of gender-affirming hormones on bone density was reported in 3 studies (Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017). Although these studies did not include a control group, comparisons to a reference population are reported using z-scores. Comparisons were made to a cisgender population, meaning for example that bone density in transfemales was compared with bone density in cisgender males. The authors of Klink et al. 2015 note that this may not be the ideal comparison, because androgens and oestrogens affect bone differently, and that bone properties in a trans population differ from their age- and sex assigned at birth-matched controls. Beyond this, a major limitation when trying to determine the impact of gender-affirming hormones on the short- and long-term bone health of children and adolescents is the lack of data on fracture rates and other patient-orientated outcomes, including rates of osteoporosis. Studies of GnRH analogues in children and adolescents with gender dysphoria suggest that GnRH analogue treatment may reduce the expected increase in bone density (which is expected during puberty). Although improvements in bone density were reported following treatment with gender-affirming hormones, Z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population.

One study reported on cardiovascular risk factors at age 22 years in people who started gender-affirming hormones for gender dysphoria as adolescents. While glucose levels, insulin levels and insulin resistance were broadly unchanged at 22 years, statistically

significant increases in blood pressure and body mass index were seen. A small but statistically significant worsening of the lipid profile in transmales who received testosterone was also seen at age 22 years. However, further studies with a considerably longer follow-up and a focus on patient-oriented outcomes, including cardiovascular events and mortality are needed to determine the long-term impact on cardiovascular health of starting gender-affirming hormones during childhood and adolescence.

Only 1 study reported adverse events and discontinuation rates with gender-affirming hormones in children and adolescents. Conclusions on these outcomes cannot be made based on this study alone.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

7. Conclusion

This evidence review found limited evidence for the effectiveness and safety of gender-affirming hormones in children and adolescents with gender dysphoria, with all studies being uncontrolled, observational studies, and all outcomes of very low certainty. Any potential benefits of treatment must be weighed against the largely unknown long-term safety profile of these treatments.

The results from 5 uncontrolled, observational studies (Achille et al. 2020, Allen et al. 2019, Kaltiala et al. 2020. Kuper et al. 2020, Lopez de Lara et al. 2020) suggest that, in children and adolescents with gender dysphoria, gender-affirming hormones are likely to improve symptoms of gender dysphoria, and may also improve depression, anxiety, quality of life, suicidality, and psychosocial functioning. The impact of treatment on body image is unclear. All results were of very low certainty. The clinical relevance of any improvements to the person is difficult to determine because most outcomes do not have a recognised minimal clinically important difference, and the authors do not present statistical analysis for some outcomes.

A further 5 uncontrolled, observational studies (Khatchadourian et al. 2014, Klaver et al. 2020, Klink et al. 2015, Stoffers et al. 2019 and Vlot et al. 2017) reported on safety outcomes, all of which provided very low certainty evidence. Statistically significant increases in some measures of bone density were seen following treatment with gender-affirming hormones, although results varied by bone region (lumber spine versus femoral neck) and by population (transfemales versus transmales). However, z-scores suggest that bone density remained lower in transfemales and transmales compared with an equivalent cisgender population. Results from 1 study of gender-affirming hormones started during adolescence reported statistically significant increases in blood pressure and body mass index, and worsening of the lipid profile (in transmales) at age 22 years, although longer term studies that report on cardiovascular event rates are needed. Adverse events and discontinuation rates associated with gender-affirming hormones were only reported in 1 study, and no conclusions can be made on these outcomes.

This review did not identify sub-groups of people who may benefit more from gender-affirming hormones. Limited evidence from 2 studies suggests there was no difference in

response to treatment between transfemales and transmales for mental health and quality of life (Achille et al. 2020 and Allen et al. 2019).

No cost-effectiveness evidence was found to determine whether gender-affirming hormones are a cost-effective treatment for children and adolescents with gender dysphoria.

Appendix A PICO

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of gender-affirming hormones compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   (a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   (b) what were the ages at which participants commenced treatment with gender-affirming hormones?
   (c) what was the duration of GnRH analogues treatment?

PICO table

P –Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by the study. The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered: • Sex assigned at birth males • Sex assigned at birth females

	• The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months) • The age at which treatment was initiated with GnRH analogues and with gender-affirming hormones. • The age of onset of gender dysphoria • The age of onset of puberty • Adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Gender-affirming hormone treatments: • A testosterone preparation for sex assigned at birth female patients which may include testosterone in the form of Sustanon injections*; testosterone enantate injections; Tostran gel*; Testogel; Testim gel; oral testosterone capsules in the form of testosterone undecanoate (Restandol); Andriol testocaps; Nebido • An oestradiol preparation** for sex assigned at birth male patients which may include: oral estradiol valerate*; oestrogen patches (7β-oestradiol patches e.g. Evorel or Estradem); Estradot patches; ethinyloestradiol *** *These are the used by Leeds Hospital, England. ** Be aware that the American spelling is oestrogen without the 'o'. ***Ethinyloestradiol is rarely used.
C – Comparator(s)	One or a combination of: • Psychological support • Social transitioning to the gender with which the individual identifies. No intervention
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with gender-affirming hormones was initiated • The length of treatment with GnRH analogues where possible. **A: Clinical Effectiveness** *Critical to decision making* • **Impact on gender dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender

	Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measure. • **Impact on Quality of Life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measures. *Important to decision making* • **Impact on body image** This outcome is important because some young people with gender dysphoria may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender. The Body Image Scale could be used as a measure. Other measures as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial Impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up and should also be ascertained as part of this outcome.

	Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery - Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may in adulthood proceed to transitioning surgery. Stated measures of the extent of surgery and satisfaction with surgery in studies may be reported. • **De-transition** The proportion of patients who de-transition following the commencement of gender-affirming hormone treatment and the reasons why. This outcome is important to patients because there is uncertainty about the short and long term safety and adverse effects of gender-affirming hormones in children and adolescents with gender dysphoria. **B: Safety** • Short and long -term safety and adverse effects of taking gender-affirming hormones is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long term effects that may impact on decisions for transitioning or de-transitioning. Aspects to be reported on should include Impact of the drug use such as clinically relevant derangement in renal and liver function tests, lipids, glucose, insulin and glycosylated haemoglobin, cognitive development and functioning. The clinical and physical impact of temporary and permanent withdrawal the drug such as when patients decide to de-transition – e.g. delay in the attainment of peak bone mass, attenuation of peak bone mass, permanent physical effects. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 21 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines, pre-publication prints, case reports and resource utilisation studies were excluded.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search date: 21 Jul 2020
Number of results retrieved: 650
Search strategy:
Database: Ovid MEDLINE(R) <1946 to July 17, 2020>
Search Strategy:
---
1 Gender Dysphoria/ (485)
2 Gender Identity/ (18431)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3134)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (835)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7223)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12665)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102312)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6969)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114785)
13 or/1-12 (252562)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137237)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852126)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1912796)
17 Minors/ (2572)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2360626)
19 exp pediatrics/ (58102)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (835833)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2023650)
22 Puberty/ (13277)

23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424041)
24 Schools/ (38087)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468784)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89314)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887443)
29 or/14-28 (5532185)
30 13 and 29 (79220)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79220)
33 Hormones/ad, tu, th (4514)
34 exp Progesterone/ad, tu, th (10899)
35 exp Estrogens/ad, tu, th (28936)
36 exp Gonadal Steroid Hormones/ad, tu, th (34137)
37 (progesteron* or oestrogen* or estrogen*).tw. (196074)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (544)
39 exp Estradiol/ad, tu, th (10823)
40 exp Testosterone/ad, tu, th (8318)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (74936)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (90464)
43 or/33-42 (304239)
44 32 and 43 (3183)
45 limit 44 to yr="2000 -Current" (2019)
46 animals/ not humans/ (4685420)
47 45 not 46 (1194)
48 limit 47 to english language (1155)
49 (MEDLINE or pubmed).tw. (163678)
50 systematic review.tw. (121198)
51 systematic review.pt. (130231)
52 meta-analysis.pt. (117148)
53 intervention$.ti. (123904)
54 or/49-53 (380217)
55 randomized controlled trial.pt. (509468)
56 randomi?ed.mp. (796957)
57 placebo.mp. (194937)
58 or/55-57 (848627)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (5562241)
60 ((control and (group* or study)) or (time and factors)).mp. (3274107)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (4624419)
62 or/59-61 (9030680)
63 Observational Studies as Topic/ (5177)
64 Observational Study/ (81866)
65 Epidemiologic Studies/ (8358)

66 exp Case-Control Studies/ (1090891)
67 exp Cohort Studies/ (2011414)
68 Cross-Sectional Studies/ (332273)
69 Controlled Before-After Studies/ (526)
70 Historically Controlled Study/ (185)
71 Interrupted Time Series Analysis/ (913)
72 Comparative Study.pt. (1866044)
73 case control$.tw. (112152)
74 case series.tw. (59119)
75 (cohort adj (study or studies)).tw. (170281)
76 cohort analy$.tw. (6758)
77 (follow up adj (study or studies)).tw. (45131)
78 (observational adj (study or studies)).tw. (86247)
79 longitudinal.tw. (204239)
80 prospective.tw. (495367)
81 retrospective.tw. (442876)
82 cross sectional.tw. (284856)
83 or/63-82 (4368140)
84 54 or 58 or 62 or 83 (9402123)
85 48 and 84 (683)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (33)
87 85 not 86 (650)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 122
Search strategy:
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 17, 2020>
Search Strategy:
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1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1473)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2315)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20821)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (963)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15453)
13 or/1-12 (39735)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80295)

16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (320315)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119124)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (59969)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (68979)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10287)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112220)
29 or/14-28 (523053)
30 13 and 29 (9143)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9144)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (13291)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (241)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (5458)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (4772)
43 or/33-42 (19706)
44 32 and 43 (316)
45 limit 44 to yr="2000 -Current" (303)
46 animals/ not humans/ (1)
47 45 not 46 (303)
48 limit 47 to english language (303)
49 (MEDLINE or pubmed).tw. (36030)
50 systematic review.tw. (29830)
51 systematic review.pt. (1007)
52 meta-analysis.pt. (49)
53 intervention$.ti. (21354)
54 or/49-53 (68976)
55 randomized controlled trial.pt. (277)
56 randomi?ed.mp. (74978)
57 placebo.mp. (18290)
58 or/55-57 (81427)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (455)

60 ((control and (group* or study)) or (time and factors)).mp. (214372)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (339764)
62 or/59-61 (507046)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (91)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (1)
67 exp Cohort Studies/ (1)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (46)
73 case control$.tw. (14451)
74 case series.tw. (13070)
75 (cohort adj (study or studies)).tw. (29119)
76 cohort analy$.tw. (1039)
77 (follow up adj (study or studies)).tw. (3540)
78 (observational adj (study or studies)).tw. (17421)
79 longitudinal.tw. (34485)
80 prospective.tw. (63689)
81 retrospective.tw. (73761)
82 cross sectional.tw. (60195)
83 or/63-82 (250805)
84 54 or 58 or 62 or 83 (687622)
85 48 and 84 (126)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (4)
87 85 not 86 (122)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search date: 21 July 2020
Number of results retrieved: 32
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <July 17, 2020>
Search Strategy:
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1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (430)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (637)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1499)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (179)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2460)

13 or/1-12 (4883)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15416)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53285)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22649)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13005)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12420)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1407)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20083)
29 or/14-28 (87968)
30 13 and 29 (1618)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1618)
33 Hormones/ad, tu, th (0)
34 exp Progesterone/ad, tu, th (0)
35 exp Estrogens/ad, tu, th (0)
36 exp Gonadal Steroid Hormones/ad, tu, th (0)
37 (progesteron* or oestrogen* or estrogen*).tw. (1876)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (63)
39 exp Estradiol/ad, tu, th (0)
40 exp Testosterone/ad, tu, th (0)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (846)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (665)
43 or/33-42 (2850)
44 32 and 43 (64)
45 limit 44 to yr="2000 -Current" (61)
46 animals/ not humans/ (0)
47 45 not 46 (61)
48 limit 47 to english language (61)
49 (MEDLINE or pubmed).tw. (7948)
50 systematic review.tw. (7508)
51 systematic review.pt. (28)
52 meta-analysis.pt. (37)
53 intervention$.ti. (4267)
54 or/49-53 (15048)
55 randomized controlled trial.pt. (1)

56 randomi?ed.mp. (14113)
57 placebo.mp. (3097)
58 or/55-57 (15128)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (34)
60 ((control and (group* or study)) or (time and factors)).mp. (31615)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (65735)
62 or/59-61 (88222)
63 Observational Studies as Topic/ (0)
64 Observational Study/ (4)
65 Epidemiologic Studies/ (0)
66 exp Case-Control Studies/ (0)
67 exp Cohort Studies/ (0)
68 Cross-Sectional Studies/ (0)
69 Controlled Before-After Studies/ (0)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (0)
72 Comparative Study.pt. (0)
73 case control$.tw. (2577)
74 case series.tw. (2480)
75 (cohort adj (study or studies)).tw. (7959)
76 cohort analy$.tw. (287)
77 (follow up adj (study or studies)).tw. (632)
78 (observational adj (study or studies)).tw. (3763)
79 longitudinal.tw. (7079)
80 prospective.tw. (12148)
81 retrospective.tw. (16600)
82 cross sectional.tw. (9459)
83 or/63-82 (48534)
84 54 or 58 or 62 or 83 (119752)
85 48 and 84 (32)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (32)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 22 July 2020
Number of results retrieved: 3
Search strategy

Database: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search Strategy:
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1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (22)

9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Hormones/ad, tu, th (3)
34 exp Progesterone/ad, tu, th (3)
35 exp Estrogens/ad, tu, th (8)
36 exp Gonadal Steroid Hormones/ad, tu, th (22)
37 (progesteron* or oestrogen* or estrogen*).tw. (161)
38 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (3)
39 exp Estradiol/ad, tu, th (8)
40 exp Testosterone/ad, tu, th (8)
41 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (79)
42 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (61)
43 or/33-42 (261)
44 32 and 43 (7)
45 limit 44 to yr="2000 -Current" (7)
46 animals/ not humans/ (3647)
47 45 not 46 (6)
48 limit 47 to english language (6)
49 (MEDLINE or pubmed).tw. (529)
50 systematic review.tw. (512)

51 systematic review.pt. (522)
52 meta-analysis.pt. (370)
53 intervention$.ti. (247)
54 or/49-53 (1065)
55 randomized controlled trial.pt. (595)
56 randomi?ed.mp. (1203)
57 placebo.mp. (219)
58 or/55-57 (1234)
59 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ (7958)
60 ((control and (group* or study)) or (time and factors)).mp. (4307)
61 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (5828)
62 or/59-61 (11814)
63 Observational Studies as Topic/ (27)
64 Observational Study/ (449)
65 Epidemiologic Studies/ (7)
66 exp Case-Control Studies/ (2173)
67 exp Cohort Studies/ (3287)
68 Cross-Sectional Studies/ (837)
69 Controlled Before-After Studies/ (1)
70 Historically Controlled Study/ (0)
71 Interrupted Time Series Analysis/ (6)
72 Comparative Study.pt. (768)
73 case control$.tw. (182)
74 case series.tw. (139)
75 (cohort adj (study or studies)).tw. (561)
76 cohort analy$.tw. (22)
77 (follow up adj (study or studies)).tw. (40)
78 (observational adj (study or studies)).tw. (253)
79 longitudinal.tw. (429)
80 prospective.tw. (778)
81 retrospective.tw. (1032)
82 cross sectional.tw. (739)
83 or/63-82 (5471)
84 54 or 58 or 62 or 83 (12581)
85 48 and 84 (3)
86 limit 85 to (letter or historical article or comment or editorial or news or case reports) (0)
87 85 not 86 (3)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23 July 2020
Number of results retrieved: 1207
Search strategy:

Database: Embase <1974 to 2020 July 22>
Search Strategy:
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1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)

6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ (1108)
8 (gender* adj3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (12470)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (581748)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ or adolescent health/ or middle school student/ or high school student/ (3440943)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)
25 or/14-24 (7130881)
26 13 and 25 (181778)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (17)
28 26 or 27 (181778)
29 hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (5160)
30 exp progesterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (23479)
31 exp estrogen/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (57641)
32 steroid hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (372)
33 sex hormone/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (1984)
34 hormonal therapy/ (42222)
35 (progesteron* or oestrogen* or estrogen*).tw. (254142)
36 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (1224)
37 exp estradiol derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (30740)

38 exp testosterone derivative/bd, ad, an, cr, do, it, dt, to, ei, ih, ia, ar, cv, dl, im, na, ip, ut, va, iv, ve, vi, po, pa, pr, sc, li, th, tp, td (15868)
39 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (99596)
40 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (114290)
41 or/29-40 (438737)
42 28 and 41 (6053)
43 limit 42 to yr="2000 -Current" (4741)
44 nonhuman/ not human/ (4649157)
45 43 not 44 (3636)
46 limit 45 to english language (3513)
47 (MEDLINE or pubmed).tw. (261145)
48 exp systematic review/ or systematic review.tw. (302985)
49 meta-analysis/ (191173)
50 intervention$.ti. (200041)
51 or/47-50 (660206)
52 random:.tw. (1552336)
53 placebo:.mp. (455979)
54 double-blind:.tw. (210671)
55 or/52-54 (1807280)
56 cohort analysis/ (596360)
57 exp epidemiology/ (3434332)
58 exp clinical trial/ (1504711)
59 evaluation study/ (45870)
60 statistics/ (301181)
61 ((control and (group* or study)) or (time and factors)).mp. (3324555)
62 (program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (6067112)
63 or/56-62 (11048972)
64 Clinical study/ (155444)
65 Case control study/ (157943)
66 Family study/ (26047)
67 Longitudinal study/ (141660)
68 Retrospective study/ (937696)
69 comparative study/ (859061)
70 Prospective study/ (613138)
71 Randomized controlled trials/ (182542)
72 70 not 71 (606604)
73 Cohort analysis/ (596360)
74 cohort analy$.tw. (13020)
75 (Cohort adj (study or studies)).tw. (302159)
76 (Case control$ adj (study or studies)).tw. (137432)
77 (follow up adj (study or studies)).tw. (63423)
78 (observational adj (study or studies)).tw. (168428)
79 (epidemiologic$ adj (study or studies)).tw. (106448)
80 (cross sectional adj (study or studies)).tw. (220073)
81 case series.tw. (104089)
82 prospective.tw. (861922)
83 retrospective.tw. (886445)
84 or/64-69,72-83 (4047788)
85 51 or 55 or 63 or 84 (12494560)
86 46 and 85 (2151)
87 86 not (letter or editorial).pt. (2137)

88 87 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (1207)

Database: APA PsycInfo

Platform: Ovid
Version: APA PsycInfo <1806 to July Week 2 2020>
Search date: 22 July 2020
Number of results retrieved: 581
Search strategy:

Database: APA PsycInfo <1806 to July Week 2 2020>
Search Strategy:
---
1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15276)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99498)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)
14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ (29181)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1765408)
26 11 and 25 (49560)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)

28 26 or 27 (49561)
29 hormones/ (8408)
30 sex hormones/ (1777)
31 exp progestational hormones/ (2409)
32 estrogens/ (3889)
33 steroids/ (3797)
34 (progesteron* or oestrogen* or estrogen*).tw. (11188)
35 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. (457)
36 estradiol/ (3120)
37 testosterone/ (5606)
38 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. (9625)
39 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. (6741)
40 or/29-39 (30344)
41 28 and 40 (1005)
42 limit 41 to yr="2000 -Current" (749)
43 limit 42 to english language (692)
44 limit 43 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (111)
45 43 not 44 (581)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 22 July 2020
Number of results retrieved: CDSR 0 ; CENTRAL 67.

ID Search Hits
#1 MeSH descriptor: [Gender Dysphoria] this term only 3
#2 MeSH descriptor: [Gender Identity] this term only 227
#3 MeSH descriptor: [Sexual and Gender Disorders] this term only 2
#4 MeSH descriptor: [Transsexualism] this term only 27
#5 MeSH descriptor: [Transgender Persons] this term only 36
#6 MeSH descriptor: [Health Services for Transgender Persons] this term only 0
#7 MeSH descriptor: [Sex Reassignment Procedures] explode all trees 4
#8 (gender* near/3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab,kw 702
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab,kw 959
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab,kw 3969
#11 ((sex or gender*) near/3 (reassign* or chang* or transform* or transition*)):ti,ab,kw 524
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab,kw 516
#13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 6413
#14 MeSH descriptor: [Infant] explode all trees 28440
#15 MeSH descriptor: [Infant Health] this term only 49
#16 MeSH descriptor: [Infant Welfare] this term only 82

#17 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab,kw,so 89530
#18 MeSH descriptor: [Child] explode all trees 44089
#19 MeSH descriptor: [Child Behavior] explode all trees 2061
#20 MeSH descriptor: [Child Health] this term only 98
#21 MeSH descriptor: [Child Welfare] this term only 325
#22 MeSH descriptor: [Minors] this term only 8
#23 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw,so 265417
#24 MeSH descriptor: [Pediatrics] explode all trees 661
#25 (pediatric* or paediatric* or peadiatric*):ti,ab,kw,so 57725
#26 MeSH descriptor: [Adolescent] this term only 102154
#27 MeSH descriptor: [Adolescent Behavior] this term only 1358
#28 MeSH descriptor: [Adolescent Health] this term only29
#29 MeSH descriptor: [Puberty] this term only 295
#30 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab,kw,so 140927
#31 MeSH descriptor: [Schools] this term only 1914
#32 MeSH descriptor: [Child Day Care Centers] this term only 231
#33 MeSH descriptor: [Nurseries, Infant] explode all trees 17
#34 MeSH descriptor: [Schools, Nursery] this term only 37
#35 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw,so 97810
#36 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near/2 (year or years or age or ages or aged)):ti,ab 6710
#37 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near/2 (year or years or age or ages or aged)):ti,ab 196881
#38 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 516067
#39 #13 and #38 2488
#40 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab,kw 0
#41 #39 or #40 2488
#42 MeSH descriptor: [Hormones] this term only 2241
#43 MeSH descriptor: [Progesterone] explode all trees 3135
#44 MeSH descriptor: [Estrogens] explode all trees 1841
#45 MeSH descriptor: [Gonadal Steroid Hormones] explode all trees 10747
#46 (progesteron* or oestrogen* or estrogen*):ti,ab,kw 18387
#47 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)):ti,ab,kw 24
#48 MeSH descriptor: [Estradiol] explode all trees 4434
#49 MeSH descriptor: [Testosterone] explode all trees 2945
#50 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan):ti,ab,kw 7386
#51 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle):ti,ab,kw 11410
#52 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 31870
#53 #41 and #52 121
#54 "conference":pt or (clinicaltrials or trialsearch):so 492465
#55 #53 not #54 72

Database: HTA

Platform: Wiley
Version: up to 2018
Search date: 22nd July 2020
Number of results retrieved: 4
Search strategy:

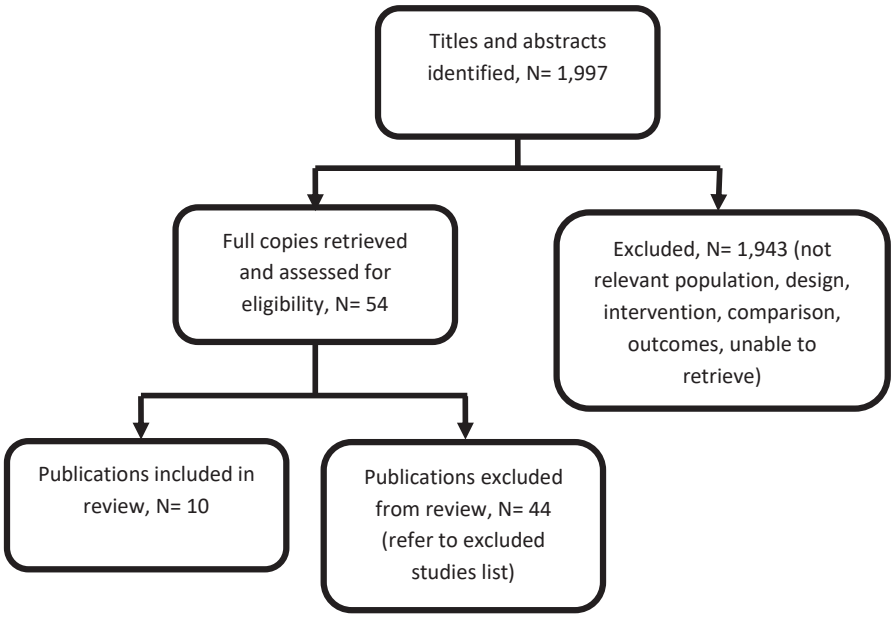
#1 MeSH DESCRIPTOR Gender Dysphoria 0
#2 MeSH DESCRIPTOR Gender Identity 12
#3 MeSH DESCRIPTOR Sexual and Gender Disorders 2
#4 MeSH DESCRIPTOR Transsexualism 12
#5 MeSH DESCRIPTOR Transgender Persons 3
#6 MeSH DESCRIPTOR Health Services for Transgender Persons 0
#7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1
#8 ((gender* near3 (dysphori* or incongru* or identi* or disorder* or confus* or minorit* or queer*))) 28
#9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
#10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
#11 (((sex or gender*) near3 (reassign* or chang* or transform* or transition*))) 24
#12 ((male-to-female or m2f or female-to-male or f2m)) 86
#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 261
#14 MeSH DESCRIPTOR Infant EXPLODE ALL TREES 2964
#15 MeSH DESCRIPTOR Infant Health 0
#16 MeSH DESCRIPTOR Infant Welfare 22
#17 ((prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*)) 5510
#18 MeSH DESCRIPTOR Child EXPLODE ALL TREES 4935
#19 MeSH DESCRIPTOR Child Behavior EXPLODE ALL TREES 64
#20 MeSH DESCRIPTOR Child Health 2
#21 MeSH DESCRIPTOR Child Welfare 80
#22 MeSH DESCRIPTOR Minors 2
#23 ((child* or minor or minors or boy* or girl* or kid or kids or young*)) 13575
#24 MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES 119
#25 ((pediatric* or paediatric* or peadiatric*)) 2842
#26 MeSH DESCRIPTOR Adolescent 4594
#27 MeSH DESCRIPTOR Adolescent Behavior 94
#28 MeSH DESCRIPTOR Adolescent Health 0
#29 MeSH DESCRIPTOR Puberty 3
#30 ((adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*)) 5621
#31 MeSH DESCRIPTOR Schools 168
#32 MeSH DESCRIPTOR Child Day Care Centers 12
#33 MeSH DESCRIPTOR Schools, Nursery 3
#34 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*)) 4454
#35 ((("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") near2 (year or years or age or ages or aged))) 380
#36 ((("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") near2 (year or years or age or ages or aged))) 7996

#37 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 22640
#38 #13 AND #37 116
#39 (#13 AND #37) IN HTA 4

Appendix C Evidence selection

The literature searches identified 1,997 references. These were screened using their titles and abstracts and 54 references were obtained and assessed for relevance. Of these, 10 references are included in the evidence review. The remaining 44 references were excluded and are listed in appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aranda G, Mora M, Hanzu FA et al. (2019) Effects of sex steroids on cardiovascular risk profile in transgender men under gender affirming hormone therapy. Endocrinologia, diabetes y nutricion 66(6): 385–392	Excluded on population – adult study, participants not 18 years or less (mean age 27.1 years).
Arnold, Justin D, Sarkodie, Eleanor P, Coleman, Megan E et al. (2016) Incidence of Venous Thromboembolism in Transgender Women	Excluded on population – adult study, participants not 18 years or less (mean age 33.2 years).

Study reference	Reason for exclusion
Receiving Oral Estradiol. The journal of sexual medicine 13(11): 1773–1777	
Asscheman, Henk, Giltay, Erik J, Megens, Jos A J et al. (2011) A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. European journal of endocrinology 164(4): 635–42	Excluded on population – although some participants started gender-affirming hormones when young, the study does not report the proportion who started treatment when 18 years or less. Mean ages at start of treatment were 31.4 years (transfemales) and 26.1 years (transmales), suggesting the majority of participants were older than 18 years at the start of treatment. Outcomes not reported separately for people aged 18 years or less.
Author not, found (2014) Hormone therapy for the treatment of gender dysphoria. Lansdale, PA: HAYES, Inc	Full text paper not available.
Baba, T., Endo, T., Honnma, H. et al. (2007) Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduction 22(4): 1011–1016	Excluded on population – although study included some younger people (age range 17 to 47), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becerra-Fernandez A, Perez-Lopez G, Roman MM et al. (2014) Prevalence of hyperandrogenism and polycystic ovary syndrome in female to male transsexuals. Endocrinologia y Nutricion: Organo de la Sociedad Espanola de Endocrinologia y Nutricion 61(7): 351–8	Excluded on population – although study included some younger people (age range 18 to 45), most participants were adults (mean age around 25 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Becker I, Auer M, Barkmann C et al. (2018) A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Archives of Sexual Behavior 47(8): 2335–2347	Excluded on population – study included people aged 14 to 21 years. Outcomes not reported separately for people aged 18 years or less. Better evidence available – only 11 participants received gender-affirming hormones. The majority of the study cohort were either pre-treatment, received puberty suppression alone, or received hormones and underwent surgery.
Chew D, Anderson J, Williams K et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4): e20173742	Excluded on better available evidence - systematic review did not meta-analyse results from. Individual studies from this systematic review are either

Study reference	Reason for exclusion
	included, or excluded because they did not meet the PICO criteria.
Connolly MD, Zervos MJ, Barone CJ 2nd et al. (2016) The Mental Health of Transgender Youth: Advances in Understanding. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 59(5): 489–495	Excluded on intervention - review did not investigate gender-affirming hormones
de Vries ALC, McGuire JK, Steensma TD et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696–704	Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported. Outcomes reported in other study (with a population that more closely matches PICO)
Elamin MB, Garcia MZ, Murad MH et al. (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clinical Endocrinology 72(1): 1–10	Exclude on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Fernandez JD and Tannock LR (2016) Metabolic effects of hormone therapy in transgender patients. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 22(4): 383–8	Excluded on population – adult study, participants not 18 years or less (mean ages 31 and 27 years).
Fighera TM, Ziegelmann PK, Da Silva TR et al. (2019) Bone mass effects of cross-sex hormone therapy in transgender people: Updated systematic review and meta-analysis. Journal of the Endocrine Society 3(5): 943–964	Excluded on population – all included studies conducted in adult population. Unclear whether hormones were started when participants were aged 18 years or less. Outcomes not reported by age at treatment initiation.
Getahun D, Nash R, Flanders WD et al. (2018) Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Annals of Internal Medicine 169(4): 205–213	Excluded on population – adult study, participants not 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, de Antonio IE et al. (2014) Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation 23(2): 669–76	Excluded on population – although study included some younger people (age range 16 to 67), most participants were adults (mean age 31.2 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Gomez-Gil E, Zubiaurre-Elorza L, Esteva I et al. (2012) Hormone-treated transsexuals report less	Excluded on population – adult study, participants not 18 years or less (mean age 24.6 years).

Study reference	Reason for exclusion
social distress, anxiety and depression. Psychoneuroendocrinology 37(5): 662–70	
Gooren LJ, van Trotsenburg MAA, Giltay EJ et al. (2013) Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. The Journal of Sexual Medicine 10(12): 3129–34	Excluded on population – study reports on cancer rates in people aged 18-80 years. The 3 cases of cancer all started gender-affirming hormone treatment >18 years.
Grimstad FW, Boskey E, Grey M (2020) New-Onset Abdominopelvic Pain After Initiation of Testosterone Therapy Among TransMasculine Persons: A Community-Based Exploratory Survey. LGBT health 7(5): Published Online:13 Jul 2020https://doi.org/10.1089/lgbt.2019.0258	Excluded on population – adult study, participants not 18 years or less.
Hannema SE, Schagen SEE, Cohen-Kettenis PT et al. (2017) Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. The Journal of Clinical Endocrinology and Metabolism 102(7): 2356–2363	Excluded on better evidence available – small study (n=28) with high drop-out rate (n=16 at final follow-up). Same outcomes reported in larger studies.
Jarin J, Pine-Twaddell E, Trotman G et al. (2017) Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics 139(5)	Excluded on population and better evidence available. Although the study included some younger people (age range 13 to 25; mean age 16 and 18), the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less. Outcomes were limited to physiological results (including haemoglobin, lipids and BMI). Follow-up only 6 months, other included studies report same outcomes with longer follow-up (12 to 31 months).
Keo-Meier CL, Herman LI, Reisner SL et al. (2015) Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. Journal of consulting and clinical psychology 83(1): 143–56	Excluded on population – although study included some younger people (age range 18 to 54), most participants were adults (mean age 26.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Klaver M, de Mutsert R, Wiepjes CM et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The Journal of Sexual Medicine 15(2): 251–260	Excluded on outcomes – reported outcomes not included in PICO document. The risk of obesity with gender-affirmed hormones was reported in an included study.
McFarlane T, Zajac JD, Cheung AS (2018) Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clinical Endocrinology 89(6): 700-711	Exclude on population – all included studies conducted in adult population.

Study reference	Reason for exclusion
Meriggiola MC, Armillotta F, Costantino A et al. (2008) Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. The Journal of Sexual Medicine 5(10): 2442–53	Excluded on population – adult study, participants not 18 years or less.
Nota NM, Wiepjes CM, de Blok, CJM et al. (2018) The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. Brain: A Journal of Neurology 141(7): 2047–2054	Excluded on population – adult study, participants not 18 years or less.
Oda H and Kinoshita T (2017) Efficacy of hormonal and mental treatments with MMPI in FtM individuals: Cross-sectional and longitudinal studies. BMC Psychiatry 17(1): 256	Excluded on population – although study included some younger people (age range 15 to 43), most participants were adults (mean age around 25.6 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.
Olson-Kennedy J, Okonta V, Clark LF et al. (2018) Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine 62(4): 397–401	Excluded on population – although study included some younger people (age range 12 to 23; mean age 18 years). Outcomes not reported separately for people aged 18 years or less. Outcomes limited to physiological results (including haemoglobin, lipids, liver enzymes and BMI). Same outcomes reported in included studies that had a less indirect population and a longer follow-up.
Ott J, Kaufmann U, Bentz K et al. (2010) Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertility and sterility 93(4): 1267–72	Excluded on population – adult study, participants not 18 years or less.
Pakpoor J, Wotton CJ, Schmierer K et al. (2016) Gender identity disorders and multiple sclerosis risk: A national record-linkage study. Multiple sclerosis. Multiple Sclerosis Journal. 22(13): 1759–1762	Excluded on population – although study included some younger people, outcomes not reported separately for people aged 18 years or less. Also exclude for intervention – unclear if people received gender-affirming hormones.
Pyra M, Casimiro I, Rusie L et al. (2020) An Observational Study of Hypertension and Thromboembolism among Transgender Patients Using Gender-Affirming Hormone Therapy. Transgender Health 5(1): 1–9	Excluded on population – adult study (age range 20-70). Age at which gender-affirming hormones started not reported.
Quiros C, Patrascioiu I, Mora M et al. (2015) Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. Endocrinologia y nutricion : organo de la Sociedad Espanola de Endocrinologia y Nutricion 62(5): 210–6	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
Rowniak S, Bolt L, Sharifi C (2019) Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. JBI Database of Systematic Reviews and Implementation Reports 17(9): 1826–1854	Exclude on population – all included studies conducted in adult population.
Sequeira GM, Kidd K, El Nokali NE et al. (2019) Early Effects of Testosterone Initiation on Body Mass Index in Transmasculine Adolescents. Journal of Adolescent Health 65(6): 818–820	Exclude on outcome - study only reports BMI z-score over 12 month testosterone treatment. BMI not listed as an outcome of interest in the PICO document. Other included studies have investigated the impact of gender-affirming hormone treatment on CV risk profile, including longer term obesity rates, with a longer follow-up and more participants.
Shim JY, Laufer MR, Grimstad FW (2020) Dysmenorrhea and Endometriosis in Transgender Adolescents. Journal of Pediatric and Adolescent Gynecology. Available online 11 June 2020. https://doi.org/10.1016/j.jpag.2020.06.001	Exclude on population – only 2 participants taking testosterone before diagnosis of dysmenorrhea.
Slabbekoorn D, Van Goozen SHM, Gooren, LJG et al. (2001) Effects of cross-sex hormone treatment on emotionality in transsexuals. International Journal of Transgenderism 5(3): http://www.symposion.com/ijt/ijtvo05no03_02.htm	Excluded on population – adult study (age range 21 to 28 years)
Smith YLS., Van Goozen SHM, Kuiper AJ et al. (2005) Sex reassignment: Outcomes and predictors of treatment for adolescent and adult transsexuals. Psychological Medicine 35(1): 89–99	Excluded on population – results on adults only used to assess hormone treatment.
Sutherland N, Espinel W, Grotzke M et al. (2020) Unanswered Questions: Hereditary breast and gynecological cancer risk assessment in transgender adolescents and young adults. Journal of Genetic Counseling 29(4): 625–633	Excluded on study type – narrative review of 3 case reports.
van Velzen DM, Paldino A, Klaver M et al. (2019) Cardiometabolic Effects of Testosterone in Transmen and Estrogen Plus Cyproterone Acetate in Transwomen. The Journal of Clinical Endocrinology and Metabolism 104(6): 1937–1947	Excluded on population – adult study, participants not 18 years or less.
White Hughto JM and Reisner SL (2016) A Systematic Review of the Effects of Hormone Therapy on Psychological Functioning and Quality of Life in Transgender Individuals. Transgender Health 1(1): 21–31	Exclude on population – all included studies conducted in adult population.
Wiepjes CM, de Blok CJM, Staphorsius AS et al. (2020) Fracture Risk in Trans Women and Trans Men Using Long-Term Gender-Affirming Hormonal Treatment: A Nationwide Cohort Study. Journal of Bone and Mineral Research 35(1): 64–70	Excluded on population – adult study, all participants started gender-affirming hormones after 18 years.
Wierckx K, Mueller S, Weyers S et al. (2012) Long-term evaluation of cross-sex hormone treatment in	Excluded on population – adult study, participants not 18 years or less.

Study reference	Reason for exclusion
transsexual persons. The Journal of Sexual Medicine 9(10): 2641–51	
Wierckx K, Van Caenegem E, Schreiner T et al. (2014) Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. The journal of sexual medicine 11(8): 1999–2011	Excluded on population – adult study, participants not 18 years or less.
Wilson R, Jenkins C, Miller H et al. (2006) The effect of oestrogen on cytokine and antioxidant levels in male to female transsexual patients. Maturitas 55(1): 14–8	Excluded on population – adult study, participants not 18 years or less.
Witcomb GL, Bouman WP, Claes L et al. (2018) Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. Journal of Affective Disorders 235: 308–315	Excluded on population – although study included some younger people (age range 15 to 79), most participants were adults (mean age around 30.4 years) and the proportion who started treatment when 18 years or less is not reported. Outcomes not reported separately for people aged 18 years or less.

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8 **Study location** Single centre, New York, United States **Study type** Prospective longitudinal study **Study aim** To assess the psychological wellbeing and quality of life in children and adolescents who have sought endocrine	Inclusion and exclusion not reported- it appears from the description in the publication that all people referred for gender dysphoria were invited to participate, and the vast majority agreed. Of the 95 treatment naïve people who entered the study, 50 people completed all follow-up questionnaires and were included in the analysis. No description of the 45 people without follow-up data reported. The study included 50 children, adolescents and young adults with gender dysphoria.	**Intervention** Endocrine interventions (the collective term used by authors for puberty suppression and gender-affirming hormones) were introduced as per Endocrine Society and the World Professional Association for	**Critical Outcomes** ***Impact on mental health*** Depression symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CESD-R). Statistically significant improvements in CESD-R score were observed from baseline (initial assessment; 21.4 points) to about 12 months follow-up (13.9 points; p<0.001). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.27) and transmales (p=0.43). The Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) was also used to assess depression symptoms. Depression scores improved from baseline (p< 0.001; absolute scores not reported numerically). Regression analysis, controlling for reported medicines for mental health problems and engagement in counselling, found no statistically significant change from baseline in transfemales (p=0.07) and transmales (p=0.67). Suicidal ideation measured using the additional questions from the PHQ 9_Modified for Teens, was presented in 10% (5/50) of 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: ○ 2 transmales due to concomitant mental health comorbidities ○ 1 transmale due to androgenic alopecia. ○ No transfemale stopped treatment. The authors report that all patients eventually restarted gender-affirming hormones, although they do not report how long treatment was	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. b) no – although follow-up time is reported for patients with more than 1 clinic visit, duration of treatment with gender-affirming hormones is not reported 3. c) incomplete - missing data **Overall quality is assessed as poor** 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: ○ 7 transmales had severe acne (requiring isotretinoin) ○ 1 transmale had andogenic alopecia ○ 3 transmales had mild dyslipidaemia (levels not reported) ○ 1 transmale had significant mood swings ○ No transfemales had minor complications	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/m^2 body surface area every 2 weeks intramuscularly,	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Safety*** Safety outcomes reported separately for transfemales and transmales. **For transfemales**, from the start of gender-affirming hormone treatment to age 22 years: • Mean BMI statistically significantly increased (mean change +1.9, 95% CI 0.6 to 3.2, p<0.005; mean BMI at 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)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Full citation Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of Clinical Endocrinology and Metabolism 100(2): e270-5 **Study location** Single centre, Amsterdam, Netherlands **Study type** Retrospective longitudinal study **Study aim** To assess peak bone mass in young adults with gender dysphoria who had received GnRH analogues and gender-affirming hormones during their pubertal years. **Study dates**	34 young people with gender dysphoria who received GnRH analogues, gender-affirming hormones and gonadectomy. The study included 15 transfemales and 19 transmales; mean age at start of gender-affirming hormones was 16.6 years (SD 1.4) and 16.4 years (SD 2.3) respectively. Participants were required to meet the DSM-IV-TR criteria for gender identity disorder of adolescence. Participants were included if they had undergone gonadectomy between June 1998 and August 2012, and they were at least 21 years old when they had the surgery. Bone mineral density data were also required at the start of GnRH analogue, gender-affirming hormones and at the age of 22 years. No concomitant treatments were reported.	**Intervention** Transfemales - oral 17-β oestradiol (incremental dosing) Transmales – IM testosterone (Sustanon 250 mg/ml; incremental dosing) Median duration of treatment with gender-affirming hormones for transfemales was 5.8 years (range 3.0 to 8.0) and for transmales was 5.4 years (range 2.8 to 7.8). The GnRH analogue was SC triptorelin 3.75 mg every 4 weeks. No details of gonadectomy reported. **Comparison** No comparison group. Comparison over time reported.	**Critical outcomes** No critical outcomes reported **Important outcomes** **Safety** ***Bone density: lumbar spine*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting gender-affirming hormones to age 22 years in transfemales- Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.22 (0.02) • Age 22 years: 0.23 (0.03) • p=0.003 z-score (range) • Start of gender-affirming hormones: -0.90 (0.80) • Age 22 years: -0.78 (1.03) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales- Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.24 (0.02) • Age 22 years: 0.25 (0.28 • p=0.001 z-score (SD) • Start of gender-affirming hormones: -0.50 (0.81) • Age 22 years: -0.033 (0.95) • p=0.002	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. 3. c) follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor** Other comments: Within person comparison. Small numbers of participants in each subgroup. No

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Gonadectomy took place between June 1998 and August 2012	At the start of gender-affirming hormone treatment, in the transfemale subgroup the median Tanner P was 4 (IQR 2) and the median Tanner G was 12 (IQR 11). In the transmale subgroup the median Tanner B was 5 (IQR 2) and the median Tanner P was 5 (IQR 0).		**Lumbar spine bone mineral density (BMD)** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.84 (0.11) • Age 22 years: 0.93 (0.10) • p<0.001 z-score (range) • Start of gender-affirming hormones: -1.01 (0.98) • Age 22 years: -1.36 (0.83) • No statistically significant difference Change from starting gender-affirming hormones to age 22 years in transmales-Mean (SD); g/m^2 • Start of gender-affirming hormones: 0.91 (0.10) • Age 22 years: 0.99 (0.13) • P<0.001 z-score (range) • Start of gender-affirming hormones: -0.72 (0.99) • Age 22 years: -0.33 (1.12) • No statistically significant difference ***Bone density: femoral region, nondominant side*** **Femoral region, nondominant side BMAD** Change from starting gender-affirming hormones to age 22 years in transfemales-Mean (SD); g/m^3 • Start of gender-affirming hormones: 0.26 (0.04) • Age 22 years: 0.28 (0.05) • 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

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/cm^2: • Start of testosterone: 0.90 (±0.11) • 6 months: 0.94 (±0.10) • 12 months: 0.95 (±0.09) • 24 months: 0.95 (±0.11) z-score (±SD): • Start of testosterone: -0.81 (±1.02) • 6 months: -0.67 (±0.95) • 12 months: -0.66 (±0.81) • 24 months: -0.74 (±1.17) ***Bone mineral density (BMD): femoral neck (hip)*** There was no statistically significant difference in right or left femoral neck (hip) bone mineral density (BMD) from start of	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. b) somewhat representative 2. c) no-non exposed cohort 3. a) secure record* 4. b) no **Domain 2: Comparability** 1. c) cohorts are not comparable on the basis of the design or analysis controlled for confounders **Domain 3: Outcome** 1. b) record linkage 2. a) yes – mean duration of gender-affirming hormone treatment was 5.8 and 5.4 years. 3. a) complete follow up - all subjects accounted for **Overall quality is assessed as poor** Other comments: None Source of funding: None

			testosterone treatment to any timepoint, up to 24 months follow-up.
			Right
			Mean (±SD), g/cm^2:
			• Start of testosterone: 0.77 (±0.08)
			• 6 months: 0.84 (±0.11)
			• 12 months: 0.82 (±0.08)
			• 24 months: 0.85 (±0.11)
			z-score (±SD):
			• Start of testosterone: -0.97 (0.79)
			• 6 months: -0.54 (±0.96)
			• 12 months: -0.80 (±0.69)
			• 24 months: -0.31 (±0.84)
			Left
			Mean (±SD), g/cm^2:
			• Start of testosterone: 0.76 (±0.09)
			• 6 months: 0.83 (±0.12)
			• 12 months: 0.81 (±0.08)
			• 24 months: 0.86 (±0.09)
			z-score (±SD):
			• Start of testosterone: -1.07 (0.85)
			• 6 months: -0.62 (±1.12)
			• 12 months: -0.93 (±0.63)
			• 24 months: -0.20 (±0.70)
			
			Other safety-related outcomes
			• Alkaline phosphatase: statistically significant increases observed from start of testosterone treatment to 6 months and 12 months ($p<0.001$), although difference at 24 months was not statistically significant. Median (IQR), U/L
			  ○ Start of testosterone: 102 (78 to 136)
			  ○ 6 months: 115 (102 to 147)
			  ○ 12 months: 112 (88 to 143)
			  ○ 24 months: 81 (range 69 to 98)
			• Creatinine: statistically significant increases observed from start of 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)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• Statistically significant increase (p≤0.01) Transmales (bone age ≥14 years), change from starting gender-affirming hormones to 24 months follow-up. • Start of gender-affirming hormones: 0.30 (0.23 to 0.41) • 24-months: 0.32 (0.23 to 0.41) • Statistically significant increase (p≤0.01) z-score (range) • Start of gender-affirming hormones: -0.27 ((-1.91 to 1.29) • 24-months: 0.02 (-2.1 to 1.35) • Statistically significant increase (p≤0.05)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
    a) Truly representative (one star)
    b) Somewhat representative (one star)
    c) Selected group
    d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
    a) Drawn from the same community as the exposed cohort (one star)
    b) Drawn from a different source
    c) No description of the derivation of the non exposed cohort
3) Ascertainment of exposure
    a) Secure record (e.g., surgical record) (one star)
    b) Structured interview (one star)
    c) Written self report
    d) No description
    e) Other
4) Demonstration that outcome of interest was not present at start of study
    a) Yes (one star)
    b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
    a) The study controls for age, sex and marital status (one star)
    b) Study controls for other factors (list) _____ (one star)
    c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
    a) Independent blind assessment (one star)
    b) Record linkage (one star)
    c) Self report
    d) No description
    e) Other
2) Was follow-up long enough for outcomes to occur
    a) Yes (one star)
    b) No
    Indicate the median duration of follow-up and a brief rationale for the assessment above:_____
3) Adequacy of follow-up of cohorts
    a) Complete follow up- all subject accounted for (one star)

b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. (one star)
c) Follow up rate less than 80% and no description of those lost
d) No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix G Grade profiles

Table 2: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? - Gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria (1 uncontrolled, prospective observational study)									
Change from baseline in mean gender dysphoria score, measured using the UGDS (duration of treatment 12 months). Higher scores indicate greater gender dysphoria.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 57.1 (SD 4.1) T1 (12 months) = 14.7 (SD 3.2) Statistically significant improvement, p<0.001	Critical	VERY LOW

Abbreviations: p: p-value; SD: standard deviation; UGDS: Utrecht Gender Dysphoria Scale

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. 2020 was assessed at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 3: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health (3 uncontrolled, prospective observational studies and 2 uncontrolled, retrospective observational studies)									
Change from baseline in mean depression score, measured using the BDI-II (duration of treatment 12 months). Higher scores indicate more severe depression.									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 19.3 (SD 5.5) T1 (12 months) = 9.7 (SD 3.9) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in mean depression score, measured using the CESD-R (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 21.4 Wave 3 (approx. 12 months) = 13.9 Statistically significant improvement (p<0.001)	Critical	VERY LOW
Change from baseline in depression score, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Statistically significant reductions in mean score, p<0.001 Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	Baseline = 9.6 (SD 5.0) Follow-up = 7.4 (SD 4.5) No statistical analysis reported for the sub-group of participants receiving gender-affirming hormones	Critical	VERY LOW
Change from baseline in depression symptoms, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=106	None	Baseline = 5.9 (SD 4.1) Follow-up = 6.0 (SD 3.8)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Kuper et al. 2020							No statistical analysis reported for the sub-group of participants who received gender-affirming hormones		
Need for treatment due to depression, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 54% (28/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in anxiety score, measured using the STAI-State subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.3 (SD 9.1) T1 (12 months) = 16.8 (SD 8.1) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in anxiety score, measured using the STAI-Trait subscale (duration of treatment 12 months). Higher scores indicate more severe anxiety.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 33.0 (SD 7.2) T1 (12 months) = 18.5 (SD 8.4) Statistically significant improvement, p<0.001	Critical	VERY LOW
Change from baseline in anxiety symptoms, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 32.6 (SD 16.3) Follow-up = 28.4 (SD 15.9) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in panic symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.1 (SD 6.3) Follow-up = 7.1 (SD 6.5) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in generalised anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 10.0 (SD 5.1) Follow-up = 8.8 (SD 5.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in social anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=82	None	Baseline = 8.5 (SD 4.1) Follow-up = 7.7 (SD 4.2) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Change from baseline in separation anxiety symptoms, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=81	None	Baseline = 3.5 (SD 3.0) Follow-up = 3.1 (SD 2.5) No statistical analysis reported for the sub-group of participants	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							who received gender-affirming hormones		
Change from baseline in school avoidance, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=80	None	Baseline = 2.6 (SD 2.1) Follow-up = 2.0 (SD 2.0) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Critical	VERY LOW
Need for treatment due to anxiety, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 48% (25/52) During real life phase 15% (8/52) Statistically significant reduction (p<0.001)	Critical	VERY LOW
Change from baseline in adjusted mean suicidality score, measured using the ASQ instrument (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations[5]	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 1.11 (SE 0.22) T1 (final assessment) = 0.27 (SE 0.12) Statistically significant improvement in score from T0 to T1, p<0.001	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=50	None	Wave 1 (baseline) = 10% (5/50) Wave 3 (approx. 12 months) = 6% (3/50)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							No statistical analysis reported		
Change from baseline in suicidal ideation (passive), information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness [6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 81% (105 people) 1 month before initial assessment = 25% (33 people) Follow-up period = 38% (51 people) No statistical analysis reported	Critical	VERY LOW
Change from baseline in suicide attempts, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness[6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 15% (20 people) 3 months before initial assessment = 2% (3 people) Follow-up period = 5% (6 people) No statistical analysis reported	Critical	VERY LOW
Change from baseline in non-suicidal self-injury, information on which was collected by clinician, exact methods / tools not reported (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[4]	Serious indirectness[6]	No serious inconsistency	Not calculable	N=130	None	Lifetime = 52% (68 people) 3 months before initial assessment = 10% (13 people) Follow-up period = 17% (23 people) No statistical analysis reported	Critical	VERY LOW
Need for treatment due to suicidality / self-harm, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 35% (18/52) During real life phase	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							4% (2/52) Statistically significant reduction (p<0.001)		
Need for mental health treatment, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 50% (26/52) During real life phase 46% (24/51) No statistically significant difference (p= 0.77)	Critical	VERY LOW
Need for treatment due to conduct problems / antisocial, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 14% (7/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.18)	Critical	VERY LOW
Need for treatment due to psychotic symptoms or psychosis, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52) During real life phase 4% (2/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
Need for treatment due to substance abuse, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 4% (2/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.56)	Critical	VERY LOW
Need for treatment due to autism, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 12% (6/52) During real life phase 6% (3/52) No statistically significant difference (p= 0.30)	Critical	VERY LOW
Need for treatment due to ADHD, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 10% (5/52) During real life phase 2% (1/52) No statistically significant difference (p= 0.09)	Critical	VERY LOW
Need for treatment due to eating disorder, during and before gender identity assessment, and during real life phase (approximately 12 months follow-up)									
1 cohort study Kaltiala et al. 2020	Serious limitations[7]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During and before gender identity assessment 2% (1/52)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							During real life phase 2% (1/52) No statistically significant difference (p=1.0)		

Abbreviations: ADHD: attention deficit hyperactivity disorder; ASQ: Ask Suicide-Screening Questions; CESD-R: Center for Epidemiologic Studies Depression Scale; BDI-II: Beck Depression Inventory II (BDI-II); p: p-value; PHQ 9_Modified for Teens: Patient Health Questionnaire Modified for Teens; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; STAI: State-Trait Anxiety Inventory

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.[4] Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality).
5 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
6 Serious indirectness in Kuper et al. 2020- Outcome reported for full study cohort, of whom approximately 17% received puberty suppression alone and did not receive gender-affirming hormones
7 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 4: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Quality of life

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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change from baseline in mean quality of life score, measured using the QLES-Q-SF) (approximately 12-month follow-up). Higher scores indicated better quality of life.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=50	None	Numerical improvements in mean score reported from wave 1 (baseline) to wave 3 (approx. 12 months), but difference not statistically significant (p = 0.085) Results presented diagrammatically, numerical results for mean score not reported	Critical	VERY LOW
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicated better well-being.									
1 cohort study Allen et al. 2019	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=39	None	T0 (baseline) = 61.70 (SE 2.43) T1 (final assessment) = 70.23 (SE 2.15) Statistically significant improvement in well-being score, p<0.002	Critical	VERY LOW

Abbreviations: GWBS: General Well-Being Scale; p: p-value; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire; SE: standard error

1 Downgraded 1 level - the cohort study by Achille et al (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Serious indirectness in Achille et al. 2020 - Outcome reported for full study cohort, of whom 30% were taking no treatment or puberty suppression alone at follow-up. Results for people taking gender-affirming hormones not reported separately.
3 Downgraded 1 level - the cohort study by Allen et al. (2019) was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 5: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Body image

QUALITY	Summary of findings	IMPORTANCE	CERTAINTY

					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image *(1 uncontrolled, prospective observational study)*									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=86	None	Baseline = 70.7 (SD 15.2) Follow-up = 51.4 (SD 18.3) No statistical analysis reported for the sub-group of participants who received gender-affirming hormones	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; p: p-value; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Table 6: Question 1: For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Psychological impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Psychosocial Impact (1 uncontrolled, prospective observational study and 1 uncontrolled, retrospective observational study)									
Change from baseline in family functioning, measured using the Family APGAR test. Higher scores suggest more family dysfunction.									
1 cohort study Lopez de Lara et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 17.9 T1 (12 months) = 18.0 No statistical analysis reported	Important	VERY LOW
Change from baseline in mean patient strengths and difficulties score, measured using the SDQ, Spanish Version (total difficulties score) (duration of treatment 12 months). Higher scores suggest the presence of a behavioural disorder.									
1 cohort study	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=23	None	T0 (baseline) = 14.7 (SD 3.3) T1 (12 months) = 10.3 (SD 2.9)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lopez de Lara et al. 2020							Statistically significant improvement p<0.001		
Functioning in adolescent development: Living with parent(s)/ guardians[2] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland). Not living with parent(s) or guardian in your early 20s is a marker of age-appropriate functioning in Finnish culture.									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 73% (38/52) During real life phase = 40% (21/50) Statistically significant reduction (p=0.001)	Important	VERY LOW
Functioning in adolescent development: Normative peer contacts[4] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 89% (46/52) During real life phase = 81% (42/52) Statistically significant reduction (p<0.001)	Important	VERY LOW
Functioning in adolescent development: Progresses normatively in school/ work[5] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 64% (33/52) During real life phase = 60% (31/52) No statistically significant difference (p=0.69)	Important	VERY LOW
Functioning in adolescent development: Has been dating or had steady relationships[6] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 62% (32/50)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kaltiala et al. 2020							During real life phase = 58% (30/52) No statistically significant difference (p=0.51)		
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home[7] (outcome reported for the approximately 12-month period after starting gender-affirming hormones; referred to as the 'real-life phase' in Finland)									
1 cohort study Kaltiala et al. 2020	Serious limitations[2]	No serious indirectness	No serious inconsistency	Not calculable	N=52	None	During gender identity assessment = 81% (42/52) During real life phase = 81% (42/52) No statistically significant difference (p=1.00)	Important	VERY LOW

Abbreviations: APGAR: Adaptability, Partnership, Growth, Affection and Resolve; p: p-value; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire

1 Downgraded 1 level - the cohort study by Lopez de Lara et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
2 Living arrangements were classified as (1) living with at least one parent/guardian, (2) living in a boarding school, with an adult relative, in some form of supported accommodation or the like, where supervision and guidance by a responsible adult is provided, (3) independently alone or in a shared household with a peer, (4) with a romantic partner. In the analyses dichotomised living arrangements as (a) parent(s)/guardian(s) vs. in other arrangements.
3 Downgraded 1 level - the cohort study by Kaltiala et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding and no control group).
4 Peer relationships were classified as: (1) socialises with friends in leisure time, outside of activities supervised by adults, (2) socialises with peers only at school or in the context of rehabilitative activity, (3) spends time close to peers, for example in school or rehabilitative activity, but does not connect with them, (4) does not meet peers at all. In the analyses, peer relationships during (a) gender identity assessment and (b) the real-life phase were dichotomized to age-appropriate (normative) (1) vs. restricted or lacking (2–4).
5 School/work participation was classified as (1) age appropriate participation in mainstream curriculum, progresses without difficulties, (2) participates in mainstream curriculum with difficulty, (3) participates in rehabilitative educational or work activity, (4) not involved in education and working life. Age-appropriate participation during (1) was recorded if the adolescent attended mainstream secondary education or upper secondary education at a regular rate (a class per year in comprehensive school; has not changed more than once between tracks in upper secondary education) or had proceeded to work life after completing vocational education. Participation with difficulty (2) was recorded if the adolescent was enrolled in mainstream education but had to repeat a class, studied with special arrangements (for example, in a special small group), or followed some form of adjusted curriculum. In the analyses, school/work life during (a) gender identity assessment and (b) real-life phase was dichotomised to normative (1) vs. any other (2, 3 or 4).
6 Romantic involvement was recorded (1) has or has had a dating or steady relationship, not only online, (2) has had a romantic relationship only online, (3) has not had dating or steady relationships. In the analyses we compared has or has had (1) vs. has not had (2,3) a dating or steady relationship during (a) gender identity assessment and (b) real-life phase. Sexual history was recorded in more detail in case histories during gender identity assessment, and for this period we also collected the experiences of (French) kissing (yes/no), intercourse (yes/no) and experience of any genitally intimate contact with a partner (petting under clothes or naked, intercourse, oral sex) (yes/no).

7 In recording age-appropriate competence in managing everyday matters it was expected that early adolescents (up to 14 years) would be able, for example, to do shopping and travel alone on local public transport, and to help with household duties assigned by their parents. Middle adolescents (15–17 years) were further assumed, for example, to be able make telephone calls in matters important to them (for example, when seeking a summer job), to deal with school-related issues with school personnel without parental participation, to select and start new hobbies independently and to fulfil their role in summer jobs and in similar responsibilities of young people. Late adolescents (18 years and over), legally adults, were expected to have, in addition to the above, competence to talk to authorities such as professionals in health and social services, employment or educational institutions, to deal with banks or health insurance, to manage their financial issues and to manage their housekeeping if they chose to move to live independently of parents/guardians. Competence in managing everyday matters was recorded as follows: (1) the adolescent is able to cope age appropriately outside home, (2) the adolescent needs support in age-appropriate matters outside home but functions age-appropriately in the home (manages her/his own hygiene, clothing and nutrition, participates in (younger subjects) or takes responsibility for (older subjects) housekeeping) and (3) the adolescent's functioning is inadequate both at home and outside home. For the analyses, participants were determined to be able to age-appropriately able cope with matters outside of the home (1) vs. not (2,3).

Table 7: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Lumbar spine bone mineral apparent density (BMAD) (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=13 (Mean) N=14 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.22 (0.02) Age 22 years: 0.23 (0.03) P=0.003 z-score (SD) Start of gender-affirming hormones: -0.90 (0.80) Age 22 years: -0.78 (1.03) No statistically significant difference	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.20 (0.18 to 0.24)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							24-month follow-up (C24): 0.22 (0.19 to 0.27) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -1.52 (-2.36 to 0.42) 24-month follow-up (C24): -1.10 (-2.44 to 0.69) Statistically significant increase (p≤0.05)		
Change from baseline in lumbar spine BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.22 (0.19 to 0.24) 24-month follow-up (C24): 0.23 (0.21 to 0.26) Statistically significant increase (p≤0.05) z-score (range) Start of gender-affirming hormones (C0): -1.15 (-2.21 to 0.08) 24-month follow-up (C24): -0.66 (-1.66 to 0.54) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in lumber spine BMAD in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.24 (0.02) Age 22 years: 0.25 (0.28) P=0.001 z-score Start of gender-affirming hormones: -0.50 (0.81) Age 22 years: -0.033 (0.95) P=0.002	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/m^3 Start of gender-affirming hormones (C0): 0.23 (0.19 to 0.28) 24-month follow-up (C24): 0.25 (0.22 to 0.28) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.84 (-2.2 to 0.87) 24-month follow-up (C24): -0.15 (-1.38 to 0.94) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in lumbar spine BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m^3	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Vlot et al. 2017							Start of gender-affirming hormones (C0): 0.24 (0.20 to 0.28) 24-month follow-up (C24): 0.25 (0.21 to 0.30) Statistically significant increase (p≤0.01) z-score (range) Start of gender-affirming hormones (C0): -0.29 (-2.28 to 0.90) 24-month follow-up (C24): -0.06 (-1.75 to 1.61) Statistically significant increase (p≤0.01)		
Change in femoral neck BMAD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=14 (Mean) N=10 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.26 (0.04) Age 22 years: 0.28 (0.05) No statistically significant difference z-score (SD) Start of gender-affirming hormones: -1.57 (1.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transfemales with a bone age less than 15 years ('young'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/m^3 C0: 0.27 (0.20 to 0.33) C24: 0.27 (0.20 to 0.36)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant change z-score (range) C0: -1.32 (-3.39 to 0.21) C24: -1.30 (-3.51 to 0.92) No statistically significant change		
Change from baseline in femoral neck BMAD in transfemales with a bone age of 15 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/m^3 C0: 0.30 (0.26 to 0.34) C24: 0.29 (0.24 to 0.38) No statistically significant change z-score (range) C0: -0.36 (-1.50 to 0.46) C24: -0.56 (-2.17 to 1.29) No statistically significant change	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMAD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean) N=18 (z-score)	None	Mean (SD), g/m^3 Start of gender-affirming hormones: 0.31 (0.04) Age 22 years: 0.33 (0.05) P=0.010 z-score (SD) Start of gender-affirming hormones: -0.28 (0.74) Age 22 years: Not reported	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of less than 14 years ('young'; 24 months follow-up)									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/m^3 C0: 0.30 (0.22 to 0.35) C24: 0.33 (0.23 to 0.37) Statistically significant increase (p≤0.01) z-score (range) C0: -0.37 (-2.28 to 0.47) C24: -0.37 (-2.03 to 0.85) Statistically significant increase (p≤0.01)	Important	VERY LOW
Change from baseline in femoral neck BMAD in transmales with a bone age of 14 years or more ('old'; 24 months follow-up)									
1 cohort study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/m^3 C0: 0.30 (0.23 to 0.41) C24: 0.32 (0.23 to 0.41) Statistically significant increase (p≤0.01) z-score (range) C0: -0.27 ((-1.91 to 1.29) C24: 0.02 (-2.1 to 1.35) Statistically significant increase (p≤0.05)	Important	VERY LOW
Change in lumbar spine BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=15 (Mean) N=13 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.84 (0.11) Age 22 years: 0.93 (0.10) P<0.001 z-score (SD)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Start of gender-affirming hormones: -1.01 (0.98) Age 22 years: -1.36 (0.83) No statistically significant difference		
Change from start of gender-affirming hormones to age 22 years in lumbar spine BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean and z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.91 (0.10) Age 22 years: 0.99 (0.13) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.72 (0.99) Age 22 years: -0.33 (1.12) No statistically significant difference	Important	VERY LOW
Change from start of testosterone treatment in lumbar spine BMD in transmen (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm^2 T0: 0.90 (0.11) T6: 0.94 (0.10) T12: 0.95 (0.09) T24: 0.95 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.81 (1.02) T6: -0.67 (0.95) T12: -0.66 (0.81) T24: -0.74 (1.17)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference from T0 to any timepoint		
Change in femoral neck BMD (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transfemales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=15 (Mean) N=11 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.87 (0.08) Age 22 years: 0.94 (0.11) P=0.009 z-score (SD) Start of gender-affirming hormones: -0.95 (0.63) Age 22 years: -0.69 (0.74) No statistically significant difference	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in femoral neck BMD in transmales									
1 cohort study Klink et al. 2015	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	N=19 (Mean) N=16 (z-score)	None	Mean (SD), g/m^2 Start of gender-affirming hormones: 0.88 (0.09) Age 22 years: 0.95 (0.10) P<0.001 z-score (SD) Start of gender-affirming hormones: -0.35 (0.79) Age 22 years: -0.35 (0.74) P=0.006	Important	VERY LOW
Change from start of testosterone treatment in right femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6)	None	Mean (SD), g/cm^2 T0: 0.77 (0.08)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Stoffers et al. 2019					N=37 (T12) N=15 (T24)		T6: 0.84 (0.11) T12: 0.82 (0.08) T24: 0.85 (0.11) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -0.97 (0.79) T6: -0.54 (0.96) T12: -0.80 (0.69) T24: -0.31 (0.84) No statistically significant difference from T0 to any timepoint		
Change from start of testosterone treatment in left femoral neck (hip) BMD in transmales (follow-up 6 to 24 months)									
1 cohort study Stoffers et al. 2019	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T6) N=37 (T12) N=15 (T24)	None	Mean (SD), g/cm^2 T0: 0.76 (0.09) T6: 0.83 (0.12) T12: 0.81 (0.08) T24: 0.86 (0.09) No statistically significant difference from T0 to any timepoint z-score (SD) T0: -1.07 (0.85) T6: -0.62 (1.12) T12: -0.93 (0.63) T24: -0.20 (0.70) No statistically significant difference from T0 to any timepoint	Important	VERY LOW

Abbreviations: BMAD: bone mineral apparent density; BMD: bone mineral density; g: grams; m: metre; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)
2 Outcomes reported after gender reassignment surgery and not after gender-affirming hormones alone. Unclear whether observed changes are due to hormones or surgery
3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control)
4 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 8: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Cardiovascular risk factors

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change in body mass index (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in BMI in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +1.9 (0.6 to 3.2) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.2 (21.6 to 24.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in BMI in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +1.4 (0.8 to 2.0) Statistically significant increase (p<0.005) Mean BMI at 22 years (95% CI): 23.9 (23.0 to 24.7)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Obesity rates at age 22 years (1 uncontrolled, retrospective observational study)									
Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	At 22 years, 9.9% of transfemales were obese, compared with 3.0% in reference cisgender population No statistically analysis reported	Important	VERY LOW
Obesity rates at age 22 years in transfemales who started gender-affirming hormones as adolescents (1 uncontrolled, retrospective observational study)									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	At 22 years, 6.6% of transmales were obese, compared with 2.2% in reference cisgender population No statistically analysis reported	Important	VERY LOW
Change in blood pressure (1 uncontrolled, retrospective observational study)									
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) -3 (-8 to 2) No statistically significant difference Mean SBP at 22 years (95% CI): 117 (113 to 122)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +6 (3 to 10) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 75 (72 to 78)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in systolic blood pressure (SBP) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +5 (1 to 9) Statistically significant increase (p<0.05) Mean SBP at 22 years (95% CI): 126 (122 to 130)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in diastolic blood pressure (DBP) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +6 (4 to 9) Statistically significant increase (p<0.001) Mean DBP at 22 years (95% CI): 74 (72 to 77)	Important	VERY LOW
Change in glucose levels, insulin levels, insulin resistance and HbA1c (2 uncontrolled, retrospective observational studies)									
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.1 (-0.1 to 0.2)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference Mean glucose level at 22 years (95% CI): 5.0 (4.8 to 5.1)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transfemales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +2.7 (-1.7 to 7.1) No statistically significant difference Mean insulin level at 22 years (95% CI): 13.0 (8.4 to 17.6)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transfemales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI) +0.7 (-0.2 to 1.5) No statistically significant difference Mean HOMA-IR at 22 years (95% CI): 2.9 (1.9 to 3.9)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in glucose level (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) 0.0 (-0.2 to 0.2) No statistically significant difference	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Mean glucose level at 22 years (95% CI): 4.8 (4.7 to 5.0)		
Change from start of gender-affirming hormones to age 22 years in insulin level (mU/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -2.1 (-3.9 to -0.3) Statistically significant decrease (p<0.05) Mean insulin level at 22 years (95% CI): 8.6 (6.9 to 10.2)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in insulin resistance (HOMA-IR) in transmales. Higher scores indicate more insulin resistance.									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): -0.5 (-1.0 to -0.1) Statistically significant decrease (p<0.05) Mean HOMA-IR at 22 years (95% CI): 1.8 (1.4 to 2.2)	Important	VERY LOW
Change from start of testosterone in HbA1c in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW

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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=71	None	Mean change (95% CI): +0.2 (0.0 to 0.5) Statistically significant increase (p<0.05) Mean triglycerides at 22 years (95% CI): 1.1 (0.9 to 1.4)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in total cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001) Mean total cholesterol at 22 years (95% CI): 4.6 (4.3 to 4.8)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in HDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) -0.3 (-0.4 to -0.2) Statistically significant decrease (p<0.001) Mean HDL cholesterol at 22 years (95% CI): 1.3 (1.2 to 1.3)	Important	VERY LOW
Change from start of gender-affirming hormones to age 22 years in LDL cholesterol (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI): +0.4 (0.2 to 0.6) Statistically significant increase (p<0.001)	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							Mean LDL cholesterol at 22 years (95% CI): 2.6 (2.4 to 2.8)		
Change from start of gender-affirming hormones to age 22 years in triglycerides (mmol/L) in transmales									
1 cohort study Klaver et al. 2020	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=121	None	Mean change (95% CI) +0.5 (0.3 to 0.7) Statistically significant increase (p<0.001) Mean triglycerides at 22 years (95% CI): 1.3 (1.1 to 1.5)	Important	VERY LOW

Abbreviations: BMI: boss mass index; CI: confidence interval; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; HDL: high-density lipoproteins; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LDL: low-density lipoproteins; mmol/L: millimoles per litre; mU/L: milliunits per litre; SBP: systolic blood pressure; SD: standard deviation

1 Downgraded 1 level - the cohort study by Klaver et al. (2020) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
2 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)

Table 9: Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of gender-affirming hormones compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – Other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Liver enzymes (1 uncontrolled, retrospective observational study)									
Change from start of testosterone in aspartate aminotransferase (AST) level in transmales (up to 24 months follow-up)									

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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	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)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=62 (T0 and T1) N=37 (T12) N=15 (T24)	None	Mean (SD), umol/L T0: 62 (7) T6: 70 (9) T12: 74 (10) T24: 81 (10) Statistically significant increase from T0 at all timepoints (p<0.001)	Important	VERY LOW
Change from start of testosterone in serum urea[2] level in transmales (up to 24 months follow-up)									
1 cohort study Stoffers et al. 2019	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N= Not reported	None	No statistically significant change from start of testosterone treatment Numerical results, follow-up duration and further details of statistical analysis not reported.	Important	VERY LOW
Adverse effects (1 uncontrolled, retrospective observational study)									
Permanent discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	No participants permanently discontinued gender-affirming hormones.	Important	VERY LOW
Temporary discontinuation of gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian 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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							comorbidities and 1 due to androgenic alopecia. All eventually resumed treatment. No transfemales receiving oestrogen temporarily discontinued treatment		
Minor complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	12/63 participants had minor complications during treatment with gender-affirming hormones All 12 were transmales receiving testosterone. Complications were severe acne (n=7), androgenic alopecia (n=1) mild dyslipidaemia (n=3) and significant mood swings (n=1) No transfemales receiving oestrogen had minor complications	Important	VERY LOW
Severe complications during treatment with gender-affirming hormones (median follow-up 2.0 years (range 0.0 to 11.3)									
1 cohort study Khatchadourian et al. 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=63	None	No severe complications reported during gender-affirming treatment	Important	VERY LOW

Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; IQR: interquartile range; SD: standard deviation; U/L: units per litre; umol/L: micromole per litre

1 Downgraded 1 level - the cohort study by Stoffers et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group)
2 Referred to as 'ureum' in original publication
3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up)

Table 10: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Transfemales compared with transmales

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean suicidality score, measured using the ASQ tool (mean treatment duration 349 days). Higher scores indicate a greater degree of suicidality.									
1 cohort study Allen et al. 2019	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	**Transfemales** T0 (baseline) = 1.21 (SE 0.36) T1 (final assessment) = 0.24 (SE 0.19) **Transmales** T0 (baseline) = 1.01 (SE 0.23) T1 (final assessment) = 0.29 (SE 0.13) No statistically significant difference in change from baseline between transfemales and transmales (p=0.79)	Critical	VERY LOW
Impact on quality of life (1 uncontrolled, retrospective observational study)									
Change from baseline in adjusted mean well-being score, measured using the GWBS of the Pediatric Quality of Life Inventory (mean treatment duration 349 days). Higher scores indicate better well-being.									
1 cohort study Allen et al. 2019	Serious limitations[4]	No serious indirectness	No serious inconsistency	Not calculable	N=14	N=33	**Transfemales** T0 (baseline) = 58.44 (SE 4.09) T1 (final assessment) = 69.52 (SE 3.62) **Transmales** T0 (baseline) = 64.95 (SE 2.66)	Critical	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Transfemales	Transmales	Result (95% CI)		
							T1 (final assessment) = 70.94 (SE 2.35) No statistically significant difference in change from baseline between transfemales and transmales (p=0.32)		

Abbreviations: ASQ: Ask Suicide-Screening Questions; GWBS: General Well-Being Scale; SE: standard error

1 The cohort study by Allen et al. 2019 was assessed at high risk of bias (poor quality; lack of blinding and no control group).

Table 11: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth males (transfemales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=40	None	Baseline = 7.5 (SD 4.9) Follow-up = 6.6 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transfemales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study 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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean anxiety symptoms in transfemales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 26.4 (SD 14.2) Follow-up = 24.3 (SD 15.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 5.7 (SD 4.9) Follow-up = 5.1 (SD 4.9) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 8.6 (SD 5.1) Follow-up = 8.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean social anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 7.1 (SD 3.9) Follow-up = 6.8 (SD 4.4) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean separation anxiety symptoms in transfemales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=34	None	Baseline = 3.4 (SD 3.3) Follow-up = 2.7 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW
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.									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study type and number of studies Author year	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=33	None	Baseline = 1.8 (SD 1.7) Follow-up = 1.9 (SD 2.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transfemales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	Wave 1 (baseline) = 11.8% (2/17) Wave 2 (approx. 12 months) = 5.9% (1/17) No statistical analysis reported	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image in transfemales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=30	None	Baseline = 67.5 (SD 19.5) Follow-up = 49.0 (SD 21.6) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 12: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Sex assigned at birth females (transmales)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), self-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=76	None	Baseline = 10.4 (SD 5.0) Follow-up = 7.5 (SD 4.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean depression symptoms in transmales, measured using the Quick Inventory of Depressive Symptoms (QIDS), clinician-reported (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe depression.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=78	None	Baseline = 6.7 (SD 4.4) Follow-up = 6.2 (SD 4.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean anxiety symptoms in transmales, measured using the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe anxiety.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 35.4 (SD 16.5) Follow-up = 29.8 (SD 15.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean panic symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 9.3 (SD 6.5) Follow-up = 7.9 (SD 6.5) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean generalised anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 10.4 (SD 5.0) Follow-up = 9.0 (SD 5.1) No statistical analysis reported for this sub-group	Critical	VERY LOW
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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Kuper et al. 2020							No statistical analysis reported for this sub-group		
Change from baseline in mean separation anxiety symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 4.2 (SD 3.4) Follow-up = 3.4 (SD 2.6) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in mean school avoidance symptoms in transmales, measured using specific questions from the SCARED questionnaire (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores indicate more severe symptoms.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=65	None	Baseline = 2.9 (SD 2.3) Follow-up = 2.0 (SD 2.3) No statistical analysis reported for this sub-group	Critical	VERY LOW
Change from baseline in percentage of participants with suicidal ideation in transmales, measured using the additional questions from the PHQ 9_Modified for Teens (approximately 12-month follow-up)									
1 cohort study Achille et al. 2020	Serious limitations[2]	Serious indirectness[3]	No serious inconsistency	Not calculable	N=33	None	Wave 1 (baseline) = 9.1% (3/33) Wave 2 (approx. 12 months) = 6.1% (2/33) No statistical analysis reported	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image in transmales, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=66	None	Baseline = 71.1 (SD 13.4) Follow-up = 52.9 (SD 16.8) No statistical analysis reported for this sub-group	Important	VERY LOW

Abbreviations: BIS: Body Image Scale; PHQ 9: Patient Health Questionnaire 9; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation

1 Downgraded 1 level - the cohort study by Kuper et al. (2020) was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

2 Downgraded 1 level - the cohort study by Achille et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
3 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.

Table 14: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Outcomes controlled for concurrent counselling and medicines for mental health problems

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mean depression score in transfemales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.27) Numerical scores not reported	Critical	VERY LOW
Change from baseline in mean depression score in transmales, measured using the CESD-R (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=33	None	No statistically significant change from baseline (p=0.43) Numerical scores not reported	Critical	VERY LOW
Change from baseline in depression score in transfemales, measured using the Patient Health Questionnaire Modified for Teens (PHQ 9_Modified for Teens) (approximately 12-month follow-up; controlled for engagement in counselling and medicines for mental health problems). Higher scores indicate more severe depression.									
1 cohort study Achille et al. 2020	Serious limitations[1]	Serious indirectness[2]	No serious inconsistency	Not calculable	N=17	None	No statistically significant change from baseline (p=0.07) Numerical scores not reported	Critical	VERY LOW
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

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

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
							No statistically significant difference p=0.06		
Functioning in adolescent development: Progresses normatively in school/ work during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 42% (10/24) functioning well Did not need mental health treatment: 74% (20/27) functioning well Statistically significant difference p=0.02	Important	VERY LOW
Functioning in adolescent development: Is age-appropriately able to deal with matters outside of the home during the real-life phase – impact on need for mental health treatment during the real-life phase									
1 cohort study Kaltiala et al. 2020	Serious limitations[3]	No serious indirectness	No serious inconsistency	Not calculable	N=51	None	Needed mental health treatment: 67% (16/24) managing well Did not need mental health treatment: 93% (25/27) managing well Statistically significant difference p=0.02	Important	VERY LOW

Abbreviations: CESD-R: Center for Epidemiologic Studies Depression; p: p-value; PHQ 9: Patient Health Questionnaire 9; QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire

1 Downgraded 1 level - the cohort study by Achille et al 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).
2 Serious indirectness in Achille 2020- Approximately 30% of the full sample received puberty suppression alone or were receiving no treatment at final follow-up.
3 Downgraded 1 level - the cohort study by Kaltiala et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding and no control).

Table 15: From the evidence selected, are there particular sub-groups of children and adolescents with gender dysphoria that derive comparatively more (or less) benefit from treatment with gender-affirming hormones than the wider population of children and adolescents with gender dysphoria? – Tanner age

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result (95% CI)		
Impact on mental health (1 uncontrolled, retrospective observational study)									
Change from baseline in mental health problems – depression, anxiety and anxiety-related symptoms (mean duration of gender-affirming hormone treatment was 10.9 months)									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in outcomes found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. It is unclear from the paper whether Tanner age is at initial assessment, start of GnRH analogues, start of gender-affirming hormones, or another timepoint	Critical	VERY LOW
Impact on body image (1 uncontrolled, prospective observational study)									
Change from baseline in mean body image, measured using the BIS (mean duration of gender-affirming hormone treatment was 10.9 months). Higher scores represent a higher degree of body dissatisfaction.									
1 cohort study Kuper et al. 2020	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=105	None	No difference in body image score found by Tanner age. Numerical results, statistical analysis and information on specific outcomes not reported. 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

Abbreviations: BIS: Body Image Scale

1 Downgraded 1 level - the cohort study by Kuper et al. 2020 was assessed at high risk of bias (poor quality; lack of blinding, no control group and high number of participants lost to follow-up).

Glossary

Ask Suicide-Screening Questions (ASQ)	ASQ is a four-item dichotomous (yes, no) response measure with high sensitivity, designed to identify risk of suicide. A patient is considered to have screened positive if they answered yes to any item. The authors of Allen et al. 2019 altered the fourth item of the ASQ ("Have you ever tried to kill yourself?") and prefaced it with "In the past few weeks . . ." as they were not investigating lifetime suicidality. A response of 'no' was scored as 0 and a response of 'yes' was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation.
Beck Depression Inventory-II (BDI-II)	The BDI-II is a tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63.
Body Image Scale (BIS)	The BIS is used to measure body satisfaction. The scale consists of 30 body features, which the person rates on a 5-point scale. Each of the 30 items falls into one of 3 basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction.
Bone mineral apparent density (BMAD)	BMAD is a size adjusted value of bone mineral density (BMD) incorporating bone size measurements using UK norms in growing adolescents.
Center for Epidemiologic Studies Depression scale (CESD-R)	The CESD-R is a valid, widely used tool to access depressive symptoms. The CESD-R asks about how frequently a person has felt or behaved in a certain way; with 20 questions scored from 0 score is calculated as a sum of 20 questions, ranging from 0 ("not at all or less than one day") to 3 ("5–7 days" and/or "nearly every day for 2 weeks"). Total score ranges from 0 to 60, with higher scores indicating more depressive symptoms.
Cisgender	Cisgender is a term for someone whose gender identity matches their birth-registered sex.
Family APGAR (Adaptability, Partnership, Growth, Affection and Resolve) test	The Family APGAR test is a 5-item questionnaire, with higher scores indicating better family functioning. The authors reported the following interpretation of the score: functional, 17-20 points; mildly dysfunctional, 16-13 points; moderately dysfunctional, 12-10 point; severely dysfunctional, <9 points.
Gender	The roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men.
Gender dysphoria	Discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves regarding their gender) and that person's sex assigned at birth (and the associated gender role, and/or primary and secondary sex characteristics).

General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory score	The GWBS of the Pediatric Quality of Life Inventory uses uses a 5-point response scale, contains seven items, and measures two dimensions: general wellbeing (6 items) and general health (1 item). Each item is scored from 0 to 4, and the total score is linearly transformed to a 0 to 100 scale. High scores reflect fewer perceived problems and greater well-being.
GnRH analogue	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of two gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. The reduction in LH and FSH secretion reduces oestradiol secretion from the ovaries in those whose sex assigned at birth was female and testosterone secretion from the testes in those whose sex assigned at birth was male.
Patient Health Questionnaire Modified for Teens score (PHQ 9_Modified for Teens)	The PHQ 9_Modified for Teens is a validated tool to assess depression, dysthymia and suicide risk. The tool consists of 9 questions scored from 0 to 3 (total score 0 to 27), plus an additional 4 questions that are not scored. A score of 0 to 4 suggests no or minimal depressive symptoms, 5 to 9 mild, 10-14 moderate, 15-19 moderate and 20-27 severe symptoms.
Quick Inventory of Depressive Symptoms (QIDS)	Both the clinician- and self-reported QIDS are validated tools to assess depressive symptoms. The tool consists of 16 items, with the highest score for 9 items (sleep, weight, psychomotor changes, depressed mood, decreased interest, fatigue, guilt, concentration, and suicidal ideation) are added to give a total score ranging from 0 to 27. A score of 0 to 5 is suggestive of no depressive symptoms, 6 to 10 mild symptoms, 11 to 15 moderate symptoms, 16-20 severe symptoms and 21 to 27 very severe symptoms.
Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF)	QLES-Q-SF is a validated questionnaire, consisting of 15 questions that rate quality of life on a scale of 1 (poor) to 5 (very good).
Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire	SCARED is a validated, 41-point questionnaire, with each item scored 0 to 2. A total score of 25 or more is suggestive of anxiety disorder, with scores above 30 being more specific. Certain scores for specific questions may indicate the presence of other anxiety-related disorders: A score of 7 or more in questions related to panic disorder or significant somatic symptoms may indicate the presence of these. A score of 9 or more in questions related to generalised anxiety disorder may indicate the presence of this. A score of 5 or more in questions related to separation anxiety may indicate the presence of this. A score of 8 or more in questions related to social anxiety disorder may indicate the presence of this. A score of 3 or more in questions related to significant school avoidance may indicate the presence of this.
State-Trait Anxiety Inventory (STAI) score	STAI is a validated and commonly used measure of state anxiety (current state of anxiety) and trait anxiety (general state of calmness, confidence and security). It has 40 items, the first 20 covering state anxiety, the second 20 covering trait anxiety. STAI

	can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Each subtest (state and trait) is scored between 20 and 80, with higher scores indicating greater anxiety. There is no published minimal clinically meaningful difference (MCID) for STAI or thresholds for anxiety severity.
Strengths and Difficulties Questionnaire (SDQ, Spanish version	The SDQ, Spanish version includes 25-items covering emotional symptoms, conduct problems, hyperactivity/ inattention, peer relationship problems and prosocial behaviour. The authors state that a score of more than 20 is considered indicative of risk of having a disorder (normal: 0-15; borderline: 16-19, abnormal: 20-40).
Tanner stage	Tanner staging is a scale of physical development.
Transgender (including transmale and transfemale)	Transgender is a term for someone whose gender identity is not congruent with their birth-registered sex. A transfemale is a person who identifies as female and a transmale is a person who identifies as male.
Utrecht Gender Dysphoria Scale (UGDS)	The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. Higher scores indicate higher levels of gender dysphoria.

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ACADÉMIE NATIONALE DE MÉDECINE

Medicine and gender transidentity in children and adolescents

Press release of the French National Academy of Medicine[1]

February 25, 2022

Gender transidentity is the strong sense, for more than 6 months, of identification with a gender different from that assigned at birth. This feeling can cause a significant and prolonged suffering, which can lead to a risk of suicide (a). No genetic predisposition has been found.

The recognition of this disharmony is not new, but a very strong increase in the demand for physicians for this reason has been observed (1, 2) in North America, then in the countries of northern Europe and, more recently, in France, particularly in children and adolescents. For example, a recent study within a dozen high schools in Pittsburgh revealed a prevalence that was much higher than previously estimated in the United States (3): 10% of students declared themselves to be transgender or non-binary or of uncertain gender (b). In 2003, the Royal Children's Hospital in Melbourne had diagnosed gender dysphoria in only one child, while today it treats nearly 200.

Whatever the mechanisms involved in the adolescent – overuse of social networks, greater social acceptability, or example in the entourage - this epidemic-like phenomenon results in the appearance of cases or even clusters in the immediate surroundings (4). This primarily social problem is based, in part, on a questioning of an excessively dichotomous vision of gender identity by some young people.

The medical demand is accompanied by an increasing supply of care, in the form of consultations or treatment in specialized clinics, because of the distress it causes rather than a mental illness per se. Many medical specialties in the field of pediatrics are concerned. First of all psychiatry, then, if the transidentity appears real or if the malaise persists, endocrinology gynecology and finally surgery are concerned.

However, a great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause. In this respect, it is important to recall the recent decision (May 2021) of the Karolinska University Hospital in Stockholm to ban the use of hormone blockers.

Although, in France, the use of hormone blockers or hormones of the opposite sex is possible with parental authorization at any age, the greatest reserve is required in their use, given the

[1] This Press release, adopted by the French Academy of Medicine on February 25, 2022, by 59 votes for, 20 against and 13 abstentions, was approved, in its revised version, by the Board of Directors on February 28, 2022.

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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.

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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REPORT

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.

KEYWORDS

adolescents; assessment; children; communication; education; endocrinology; eunuch; gender diverse; health care professional; institutional settings; intersex; mental health; nonbinary; population; postoperative care; primary care; reproductive health; sexual health; SOC8; Standards of Care; surgery; terminology; transgender; voice

Table of contents

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.

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), *fa'afafine* (Samoa), *mahu* (French Polynesia, Hawai'i), *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 *akava'ine* (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

CERTIFICATE OF SERVICE

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

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