

**CLINICAL PRIORITIES ADVISORY GROUP**

**6th March 2024**

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| **Agenda Item No** |       |
| **National Programme** |  Gender |
| **Clinical Reference Group** | Children and Young People Gender |
| **URN** | 1927 |

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| **Title**  |
| Puberty Suppressing Hormones (PSH) for children and adolescents who have gender incongruence |

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| **Actions Requested** | 1.
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|  | 1. Recommend its approval as an IYSD
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| **Proposition** |
| Not recommended to be available as a routinely commissioned treatment option for the treatment of children and adolescents who have gender incongruence. |

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| **Clinical Panel recommendation** |
| **Select appropriate option:**The Clinical Panel recommended that the policy proposition progress as a not for routine commissioning policy proposition. |

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| **The committee is asked to receive the following assurance:** |
| 1. | The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report. |
| 2. | The Deputy Director Gender Programme confirms the proposition is supported by an: Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition.  |
| 3. | The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal. |
| 4. | The Director of Clinical Commissioning (Specialised Commissioning) confirms that the service and operational impacts have been completed. |

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| **The following documents are included (others available on request):** |
| 1. | Clinical Policy Proposition |
| 2. | Engagement/Consultation Report |
| 3. | Evidence Review and Public Health Evidence Reports |
| 4. | Clinical Panel Report |
| 5. | Equality and Health Inequalities Impact Assessment  |

**In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?**

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| **Outcome** | **Evidence statement** |
| **Clinical Effectiveness** |
| **Critical outcomes** |
| **Impact on gender dysphoria****Certainty of evidence: very low** | This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning.One uncontrolled, prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.The study measured the impact on gender dysphoria at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

The mean (±SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333) **(VERY LOW)**.**This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.** |
| **Impact on mental health: depression****Certainty of evidence: very low** | This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person.One uncontrolled, prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. The study provided evidence for depression measured at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

The mean (±SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [ ±6.72], p=0.004) **(VERY LOW)**.**This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.** |
| **Impact on mental health: anger****Certainty of evidence: very low** | This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person.One uncontrolled, prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger.The study provided evidence for anger measured at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

The mean (±SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503) **(VERY LOW)**.**This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.** |
| **Impact on mental health: anxiety****Certainty of evidence: very low** | This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. Anxiety was measured using the Trait Anxiety Scale of the State-Trait Personality Inventory (STAI). This is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety.The study provided evidence for anxiety at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

The mean (±SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276) (**VERY LOW)**.**This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.**  |
| **Quality of life** | This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified. |
| **Important outcomes** |
| **Impact on body image****Certainty of evidence: very low**  | This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for body image measured at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

The mean (±SD) body image (BIS) scores for were not statistically significantly different from baseline compared with follow-up for:* primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145)
* secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569)
* neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620) **(VERY LOW)**.

**This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.** |
| **Psychosocial impact: global functioning****Certainty of evidence: very low**  | This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning.One uncontrolled, observational, prospective cohort study ([de Vries et al 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) and one prospective cross-sectional cohort study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children’s Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning.One study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for global functioning (CGAS) at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

The mean (±SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005) **(VERY LOW)**. One study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points:* at baseline (T0) in both groups,
* after 6 months of psychological support in both groups (T1),
* after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and
* after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3).

The mean [±SD] CGAS score was statistically significantly higher (improved) for all adolescents (including those not receiving GnRH analogues) at T1, T2 or T3 compared with baseline (T0).For the immediately eligible group (who received GnRH analogues) versus the delayed eligible group (who did not receive GnRH analogues) there were no statistically significant differences in CGAS scores between the 2 groups at baseline T0 (n=201, p=0.23), T1 (n=201, p=0.73), T2 (n=121, p=0.49) or T3 (n=71, p=0.14) time points.For the immediately eligible group (who received GnRH analogues), the mean (±SD) CGAS score was not statistically significantly different at:* T1 compared with T0
* T2 compared with T1
* T3 compared with T2.

The mean (±SD) CGAS score was statistically significantly higher (improved) at: * T2 compared with T0 (n=60, 64.70 [±13.34] versus n=101, 58.72 [±11.38], p=0.003)
* T3 compared with T0 (n=35, 67.40 [±13.39] versus n=101, 58.72 [±11.38], p<0.001)
* T3 compared with T1 (n=35, 67.40 [±13.93] versus n=101, 60.89 [±12.17], p<0.001) **(VERY LOW)**.

**These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no** **statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.**  |
| **Psychosocial impact: psychosocial functioning****Certainty of evidence: very low**  | This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning.Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study ([de Vries et al, 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) and 1 cross-sectional observational study ([Staphorsius et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S0306453015000943?via%3Dihub)) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent’s age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range.One study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points:* before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and
* shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

At follow up, the mean (±SD) CBCL scores were statistically significantly lower (improved) compared with baseline for:* Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001
* Internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001)
* Externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001).

At follow up, the mean (±SD) YSR scores were statistically significantly lower (improved) compared with baseline for:* Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001)
* Internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001)
* Externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009).

The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017) **(VERY LOW)**.One study ([Staphorsius et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S0306453015000943?via%3Dihub)) assessed CBCL in a cohort of adolescents with gender dysphoria (transfemale: n=18, mean [±SD] age 15.1 [±2.4] years and transmale: n=22, mean [±SD] age 15.8 [±1.9] years) either receiving GnRH analogues (transfemale, n=8 and transmale, n=12), or not receiving GnRH analogues (transfemale, n=10 and transmale, n=10).The mean (±SD) CBCL scores for each group were (statistical analysis unclear):* transfemales (total) 57.8 [±9.2]
* transfemales receiving GnRH analogues 57.4 [±9.8]
* transfemales not receiving GnRH analogues 58.2 [±9.3]
* transmales (total) 60.4 [±10.2]
* transmales receiving GnRH analogues 57.5 [±9.4]
* transmales not receiving GnRH analogues 63.9 [±10.5] **(VERY LOW)**.

**These studies provide very low certainty evidence that during treatment with GnRH analogues psychosocial functioning may improve, with the proportion of adolescents in the clinical range for some CBCL and YSR scores decreasing over time.** |
| **Engagement with health care services****Certainty of evidence: very low** | This is an important outcome because patient engagement with health care services will impact on their clinical outcomes.Two uncontrolled observational cohort studies provided evidence relating to loss to follow up, which could be a marker of engagement with health care services ([Brik et al. 2018](https://link.springer.com/article/10.1007/s10508-020-01660-8) and [Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)). In one retrospective study ([Brik et al. 2018](https://link.springer.com/article/10.1007/s10508-020-01660-8)), 9 adolescents (9/214, 4.2%) who had stopped attending appointments were excluded from the study between November 2010 and July 2019 **(VERY LOW)**. One prospective study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) had evidence for a large loss to follow-up over time. The sample size at baseline (T0) and 6 months (T1) was 201, which dropped by 39.8% to 121 after 12 months (T2) and by 64.7% to 71 at 18 months follow-up (T3). No explanation of the reasons for loss to follow-up are reported **(VERY LOW)**. Due to their design there was no reported loss to follow-up in the other 3 effectiveness studies ([de Vries et al 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub); [Khatchadourian et al. 2014](https://www.sciencedirect.com/science/article/abs/pii/S0022347613013644?via%3Dihub); [Staphorsius et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S0306453015000943?via%3Dihub)).**These studies provide very low certainty evidence about loss to follow up, which could be a marker of engagement with health care services, during treatment with GnRH analogues. Due to the large variation in rates between studies no conclusions could be drawn.** |
| **Impact on extent of and satisfaction with surgery**  | This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified. |
| **Stopping treatment****Certainty of evidence: very low** | This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents with gender dysphoria.Two uncontrolled, retrospective, observational cohort studies provided evidence relating to stopping GnRH analogues. One study had complete reporting of the cohort ([Brik et al. 2018](https://link.springer.com/article/10.1007/s10508-020-01660-8)), the other ([Khatchadourian et al. 2014](https://www.sciencedirect.com/science/article/abs/pii/S0022347613013644?via%3Dihub)) had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported.Brik et al. 2018 narratively reported the reasons for stopping GnRH analogues in a cohort of 143 adolescents (38 transfemales and 105 transmales). Median age at the start of GnRH analogues was 15.0 years (range, 11.1–18.6 years) in transfemales and 16.1 years (range, 10.1–17.9 years) in transmales. Of these adolescents, 125 (87%, 36 transfemales, 89 transmales) subsequently started gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRH analogues. At the time of data collection, the median duration of GnRH analogue use was 2.1 years (1.6–2.8). During the follow-up period 6.3% (9/143) of adolescents had discontinued GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). The percentages and reasons for stopping were:* 2.8% (4/143) stopped GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria:
	+ 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues
	+ 1 transmale had hot flushes, increased migraines, fear of injections, stress at school and unrelated medical issues, and temporarily stopped treatment (after 4 months) and restarted 5 months later.
	+ 1 transmale had mood swings 4 months after starting GnRH analogues. After 2.2 years had unexplained severe nausea and rapid weight loss and discontinued GnRH analogues after 2.4 years
	+ 1 transmale stopped GnRH analogues because of inability to regularly collect medication and attend appointments for injections.
* 3.5% (5/143) stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons **(VERY LOW)**.

Khatchadourian et al. 2014 narratively reported the reasons for stopping GnRH analogues in a cohort of 26 adolescents (15 transmales and 11 transfemales), 42% (11/26) discontinued GnRH analogues during follow-up between 1998 and 2011. Of 15 transmales receiving GnRH analogues, 14 received testosterone during the observation period, of which:* 7 continued GnRH analogues after starting testosterone
* 7 stopped GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which:
	+ 5 stopped after hysterectomy and salpingo-oophorectomy
	+ 1 stopped after 2.2 years (transitioned to gender-affirming hormones)
	+ 1 stopped after <2 months due to mood and emotional lability **(VERY LOW)**.

Of 11 transfemales receiving GnRH analogues, 5 received oestrogen during the observation period, of which:* 4 continued GnRH analogues after starting oestrogen
* 1 stopped GnRH analogues when taking oestrogen (no reason reported) **(VERY LOW)**.

Of the remaining 6 transfemales taking GnRH analogues:* 1 stopped GnRH analogues after a few months due to emotional lability
* 1 stopped GnRH analogues before taking oestrogen (the following year delayed due to heavy smoking)
* 1 stopped GnRH analogues after 13 months due not to pursuing transition **(VERY LOW)**.

**These studies provide very low certainty evidence for the number of adolescents who stop GnRH analogues and the reasons for this.**  |

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| **Outcome** | **Evidence statement** |
| **Safety** |
| **Change in bone density: lumbar****Certainty of evidence: very low** | This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in lumbar bone density.Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on lumbar BMAD) between starting with a GnRH analogue and at 1 and 2 year intervals ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml)), and between starting GnRH analogues and starting gender-affirming hormones ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub)). All outcomes were reported separately for transfemales and transmales; also see subgroups table below.BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. It was reported as g/cm3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean.One retrospective observational study ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), n=70) provided non-comparative evidence on change in lumbar BMAD increase using z-scores. * The z-score for lumbar BMAD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score [±SD]: baseline 0.486 [0.809], 2 years −0.279 [0.930], p=0.000) and transmales (baseline −0.361 [1.439], 2 years −0.913 [1.318], p=0.001) (VERY LOW).
* The z-score for lumbar BMAD was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [0.154], 1 year −0.228 [1.027], p=0.000) and transmales (baseline −0.186 [1.230], 1 year −0.541 [1.396], p=0.006) (VERY LOW).
* Actual lumbar BMAD values in g/cm3 were not statistically significantly different between baseline and 1 or 2 years in transfemales or transmales (VERY LOW).

Two retrospective observational studies ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub), n=104 in total) provided non-comparative evidence on change in lumbar BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below.In Klink et al. 2015 the z-score for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.28 [±0.90], gender-affirming hormone −0.50 [±0.81], p=0.004). Actual lumbar BMAD values in g/cm3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales (VERY LOW).Vlot et al. 2017 reported change from starting GnRH analogues to starting gender-affirming hormones in lumbar BMAD by bone age. * The z-score for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.20 [−1.82 to 1.18], gender-affirming hormone −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years (VERY LOW).
* The z-score for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.05 [−0.78 to 2.94], gender-affirming hormone −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.60 to 1.80], gender-affirming hormone −0.29 [−2.28 to 0.90], p≤0.0001) (VERY LOW).
* Actual lumbar BMAD values in g/cm3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales with young or old bone age (VERY LOW).

Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on lumbar BMD) between starting GnRH analogues and either at 1 or 2 year intervals ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml)), or starting gender-affirming hormones ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818)). All outcomes were reported separately for transfemales and transmales; also see subgroups table below.One retrospective observational study ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), n=70) provided non-comparative evidence on change in lumbar BMD increase using z-scores. * The z-score for lumbar BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.130 [0.972], 2 years −0.890 [±1.075], p=0.000) and transmales (baseline −0.715 [±1.406], 2 years −2.000 [1.384], p=0.000) (VERY LOW).
* The z-score for lumbar BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline −0.016 [±1.106], 1 year −0.461 [±1.121], p=0.003) and transmales (baseline −0.395 [±1.428], 1 year −1.276 [±1.410], p=0.000) (VERY LOW).
* With the exception of transmales, where lumbar BMD in kg/m2 increased between baseline and 1 year (mean [±SD]: baseline 0.694 [±0.149], 1 year 0.718 [±0.124], p=0.006), actual lumbar BMD values were not statistically significantly different between baseline and 1 or 2 years in transfemales or between 0 and 2 years in transmales (VERY LOW).

One retrospective observational study ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818), n=34) provided non-comparative evidence on change in lumbar BMD between starting GnRH analogues and starting gender-affirming hormones. * The z-score for lumbar BMD was not statistically significantly different between starting GnRH analogue and starting gender-affirming hormone treatment in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.17 [±1.18], gender-affirming hormone −0.72 [±0.99], p<0.001) (VERY LOW).
* Actual lumbar BMD in g/cm2 was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (mean [±SD]: GnRH analogues 0.95 [±0.12], gender-affirming hormones 0.91 [±0.10], p=0.006) (VERY LOW).

**These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD).** |
| **Change in bone density: femoral****Certainty of evidence: very low** | This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in femoral bone density.Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on femoral BMAD) between starting treatment with a GnRH analogue and starting gender-affirming hormones ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub)). All outcomes were reported separately for transfemales and transmales; also see subgroups table below.One retrospective observational study ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818), n=34) provided non-comparative evidence on change in femoral area BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales.* The z-score for femoral area BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales (VERY LOW).
* Actual femoral area BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transmales or transfemales (VERY LOW).

One retrospective observational study ([Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub), n=70) provided non-comparative evidence on change in femoral neck (hip) BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below.* The z-score for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.71 [−3.35 to 0.37], gender-affirming hormone −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogue −0.44 [−1.37 to 0.93], gender-affirming hormone −0.36 [−1.50 to 0.46]) (VERY LOW).
* The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.39 to 1.32], gender-affirming hormone −0.27 [−1.91 to 1.29], p=0.002) (VERY LOW).
* Actual femoral neck BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or in transmales with a young bone age, but were statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.33 [0.25 to 0.39), gender-affirming hormone 0.30 [0.23 to 0.41], p≤0.01) (VERY LOW).

Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on femoral BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below.One retrospective observational study ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), n=70) provided non-comparative evidence on change in femoral neck BMD increase using z-scores. All outcomes were reported separately for transfemales and transmales.* The z-score for femoral neck BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001) (VERY LOW).
* The z-score for femoral neck BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline 0.157 [±0.905], 1 year −0.340 [±0.816], p=0.002) and transmales (baseline −0.863 [±1.215], 1 year −1.440 [±1.075], p=0.000) (VERY LOW).
* Actual femoral neck BMD values in kg/m2 were not statistically significantly different between baseline and 1 or 2 years in transmales or transfemales (VERY LOW).

One retrospective observational study ([Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818), n=34) provided non-comparative evidence on change in femoral area BMD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales.* The z-score for femoral area BMD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower in transmales (z-score mean [±SD]: GnRH analogue 0.36 [±0.88], gender-affirming hormone −0.35 [±0.79], p=0.001) (VERY LOW).
* Actual femoral area BMD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but were statistically significantly lower in transmales (mean [±SD] GnRH analogue 0.92 [±0.10], gender-affirming hormone 0.88 [±0.09], p=0.005) (VERY LOW).

**These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD), apart from actual femoral area BMD in transmales.** |
| **Cognitive development or functioning****Certainty of evidence: very low** | This is an important outcome because puberty is an important time for cognitive development and puberty suppression may affect cognitive development or functioning. One cross-sectional observational study ([Staphorsius et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S0306453015000943?via%3Dihub), n=70) provided comparative evidence on cognitive development or functioning in adolescents with gender dysphoria on GnRH analogues compared with adolescents with gender dysphoria not on GnRH analogues. Cognitive functioning was measured using an IQ test. Reaction time (in seconds) and accuracy (percentage of correct trials) were measured using the Tower of London (ToL) task. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. No statistical analyses or interpretation of the results in these groups were reported:* IQ in transfemales (mean [±SD] GnRH analogue 94.0 [±10.3], control 109.4 [±21.2]). IQ transmales (GnRH analogue 95.8 [±15.6], control 98.5 [±15.9].
* Reaction time in transfemales (mean [±SD] GnRH analogue 10.9 [±4.1], control: 9.9 [±3.1]). Reaction time transmales (GnRH analogue 9.9 [±3.1], control 10.0 [±2.0]).
* Accuracy score in transfemales (GnRH analogue 73.9 [±9.1], control 83.4 [±9.5]. Accuracy score in transmales (GnRH analogue 85.7 [±10.5], control 88.8 [±9.7].

**This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning. No conclusions could be drawn.** |
| **Other safety outcomes: kidney function****Certainty of evidence: very low** | This is an important outcome because if renal damage (raised serum creatinine is a marker of this) is suspected, GnRH analogues may need to be stopped.One prospective observational study ([Schagen et al. 2016](https://www.sciencedirect.com/science/article/abs/pii/S1743609516302193?via%3Dihub), n=116) provided non-comparative evidence on change in serum creatinine between starting GnRH analogues and at 1 year. All outcomes were reported separately for transfemales and transmales; also see subgroups table below.* There was no statistically significant difference between baseline and 1 year for serum creatinine in transfemales (mean [±SD] baseline 70 [±12], 1 year 66 [±13], p=0.20).
* There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [±8], 1 year 68 [±13], p=0.01).

**This study provides very low certainty evidence that GnRH analogues do not affect renal function.** |
| **Other safety outcomes: liver function****Certainty of evidence: very low** | This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, GnRH analogues may need to be stopped.One prospective observational study ([Schagen et al. 2016](https://www.sciencedirect.com/science/article/abs/pii/S1743609516302193?via%3Dihub), n=116) provided non-comparative evidence on elevated liver enzymes between starting GnRH analogues and during use. No comparative values or statistical analyses were reported.* Glutamyl transferase was not elevated at baseline or during use in any person.
* Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during use than at baseline.
* Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of use.

**This study provides very low certainty evidence (with no statistical analysis) that GnRH analogues do not affect liver function.** |
| **Other safety outcomes: adverse effects****Certainty of evidence: very low** | This is an important outcome because if there are adverse effects, GnRH analogues may need to be stopped.One uncontrolled, retrospective, observational cohort study ([Khatchadourian et al. 2014](https://www.sciencedirect.com/science/article/abs/pii/S0022347613013644?via%3Dihub)) provided evidence relating to adverse effects from GnRH analogues. It had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported.Khatchadourian et al. 2014 reported adverse effects in a cohort of 26 adolescents (15 transmales and 11 transfemales) receiving GnRH analogues. Of these:* 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated.
* 1 transmale developed leg pains and headaches, which eventually resolved
* 1 participant gained 19 kg within 9 months of starting GnRH analogues.

**This study provides very low certainty evidence about potential adverse effects of GnRH analogues. No conclusions could be drawn.** |

## In the Population what is the cost effectiveness of the Intervention compared with Comparator?

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| **Outcome** | **Evidence statement** |
| **Cost-effectiveness** | No studies were identified to assess the cost-effectiveness of GnRH analogues for children and adolescents with gender dysphoria. |

## From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

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| **Subgroup**  | **Evidence statement** |
| **Sex assigned at birth males (transfemales)****Certainty of evidence: Very low**  | Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales).**Impact on gender dysphoria**One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study.The mean (±SD) UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean UGDS score [±SD]: 47.95 [±9.70] versus 56.57 [±3.89]) and T1 (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001 **(VERY LOW)**.One further prospective observational longitudinal study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) provided evidence for the impact on gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. Sex assigned at birth males had a statistically significantly lower (improved) mean (±SD) UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001). However, it was not reported if this was baseline or follow-up **(VERY LOW)**. **These studies provide very low certainty evidence that in sex assigned at birth males (transfemales), gender dysphoria is lower than in sex assigned at birth females (transmales).****Impact on mental health** One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for the impact on mental health (depression, anger and anxiety) in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study.* The mean (±SD) depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and T1 (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057
* The mean (±SD) anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean TPI score [±SD]: 5.22 [±2.76] versus 6.43 [±2.78]) and T1 (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022
* The mean (±SD) anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and T1 (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001 **(VERY LOW)**.

**This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression. However, sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at both baseline and follow up.****Impact on body image**One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on body image in sex assigned at birth males.* The mean (±SD) BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and T1 (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]), between sex difference p=0.047
* The mean (±SD) BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and T1 (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001
* The mean (±SD) BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.60 [±0.58] versus 2.24 [±0.62]) and T1 (n=not reported, 2.32 [±0.59] versus 2.61 [±0.50]), between sex difference p=0.777 **(VERY LOW)**.

**This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.** **Psychosocial impact**One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth males.* Sex assigned at birth males had statistically higher mean (±SD) CGAS scores compared with sex assigned at birth females at both baseline (T0) (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and T1 (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021
* There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL Total T score at T0 or T1 (n=54, p=0.110)
* There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL internalising T score at T0 or T1 (n=54, p=0.286)
* Sex assigned at birth males had statistically lower mean (±SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and T1 (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015
* There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR Total T score at T0 or T1 (n=54, p=0.164)
* There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR internalising T score at T0 or T1 (n=54, p=0.825)
* Sex assigned at birth males had statistically lower mean (±SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and T1 (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004 **(VERY LOW)**.

One uncontrolled, observational, prospective cohort study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth males.* Sex assigned at birth males had statistically significant lower mean (±SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03) **(VERY LOW)**.

**These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). However, no conclusions could be drawn.****Change in bone density: lumbar**Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth males ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), [Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub)). See the safety results table above for a full description of the results.**These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales).****Change in bone density: femoral**Three uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on femoral bone density in sex assigned at birth males ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), [Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub)). See the safety results table above for a full description of the results.**These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth males (transfemales).****Cognitive development or functioning**One cross-sectional observational study ([Staphorsius et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S0306453015000943?via%3Dihub)) provided comparative evidence on cognitive development or functioning in sex assigned at birth males. See the safety results table above for a full description of the results.**This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth males (transfemales). No conclusions could be drawn.****Other safety outcomes: kidney function**One prospective observational study ([Schagen et al. 2016](https://www.sciencedirect.com/science/article/abs/pii/S1743609516302193?via%3Dihub)) provided non-comparative evidence on change in serum creatinine in sex assigned at birth males. See the safety results table above for a full description of the results.**This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth males (transfemales).** |
| **Sex assigned at birth females (transmales)****Certainty of evidence: Very low** | Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales).**Impact on gender dysphoria**One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) and one prospective observational longitudinal study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) provided evidence for gender dysphoria in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results.**These studies provide very low certainty evidence that in sex assigned at birth females (transmales), gender dysphoria is higher than in sex assigned at birth males (transfemales) at both baseline and follow up.****Impact on mental health** One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on mental health (depression, anger and anxiety) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results.**This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression. However, sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at baseline and follow up.****Impact on body image**One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence relating to the impact on body image in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results.**This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.****Psychosocial impact** One uncontrolled prospective observational longitudinal study ([de Vries et al. 2011](https://www.sciencedirect.com/science/article/abs/pii/S1743609515336171?via%3Dihub)) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth females. One uncontrolled, observational, prospective cohort study ([Costa et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S174360951534443X)) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results.**These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). However, no conclusions could be drawn.****Change in bone density: lumbar**Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth females ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), [Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub)). See the safety results table above for a full description of the results.**These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales).****Change in bone density: femoral**Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on femoral bone density in sex assigned at birth females ([Joseph et al. 2019](https://www.degruyter.com/view/journals/jpem/32/10/article-p1077.xml), [Klink et al. 2015](https://academic.oup.com/jcem/article/100/2/E270/2814818) and [Vlot et al. 2017](https://www.sciencedirect.com/science/article/abs/pii/S8756328216303337?via%3Dihub)). See the safety results table above for a full description of the results.**These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth females (transmales), apart from actual femoral area.****Cognitive development or functioning**One cross-sectional observational study ([Staphorsius et al. 2015](https://www.sciencedirect.com/science/article/abs/pii/S0306453015000943?via%3Dihub)) provided comparative evidence on cognitive development or functioning in sex assigned at birth females. See the safety results table above for a full description of the results.**This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth females (transmales). No conclusions could be drawn.****Other safety outcomes: kidney function**One prospective observational study ([Schagen et al. 2016](https://www.sciencedirect.com/science/article/abs/pii/S1743609516302193?via%3Dihub)) provided non-comparative evidence on change in serum creatinine in sex assigned at birth females (transmales). See the safety results table above for a full description of the results.**This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth females (transmales).** |
| **Duration of gender dysphoria** | No evidence was identified. |
| **Age at onset of gender dysphoria** | No evidence was identified. |
| **Age at which GnRH analogue started** | No evidence was identified. |
| **Age at onset of puberty** | No evidence was identified. |
| **Tanner stage at which GnRH analogue started** | No evidence was identified. |
| **Diagnosis of autistic spectrum disorder** | No evidence was identified. |
| **Diagnosis of mental health condition** | No evidence was identified. |

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| **Considerations from review by Rare Disease Advisory Group** |
| Not applicable |

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| **Pharmaceutical considerations**  |
| This clinical commissioning policy does not recommend puberty supressing hormones (PSHs) as a treatment option for the treatment of children and adolescents who have gender incongruence. Use of PSHs in this indication is not within the products’ marketing authorisation.  |

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| **Considerations from review by National Programme of Care** |
| The National Programme Board (NPB) for Gender Dysphoria Services on the 20th February 2024 was asked to assure the process that NHS England had followed for policy formation.The NPB includes five Patient and Public Voice members who were appointed to the NPB because of their relevant lived experience. At the meeting, the PPV members felt unable to assure some aspects of the process, as follows:*Have stakeholders and the public been given a proper opportunity to give their views on the proposal?* **Assured***Has there been a proper analysis of the submissions that were made to the public consultation?* **Not Assured***Does the report on the analysis of consultation submissions clearly explain the findings and conclusions of the analyst?* **Not Assured***Does NHS England’s draft consultation report demonstrate that NHS England has properly considered and responded to the submissions that were made to the consultation? Specifically including: has NHS England properly considered the submissions that proposed that additional research evidence should be taken into account?* **Not Assured***Has the draft EHIA been properly amended to respond to the submissions made by respondents to consultation?* **Not Assured***Does NHS England’s draft consultation report clearly explain how NHS England formed its [prospective] decision?* **Not Assured**In contrast, other members of the NPB were content to assure all aspects of the process.In the meeting, the Chair of the NPB asked PPV members for specific examples of why they felt that the process could not be assured. It was agreed that members would be given more time to give their detailed reasoning, in writing outside of the meeting. CPAG was provided with their reasons and with NHS England’s detailed response. While NHS England is greatly appreciative of the advice that the PPV members have given, it cannot, respectfully, agree that the PPV members have identified legitimate cause for not assuring the process. **CPAG is asked to:*** **Assure the process that has been followed, noting that the various functions of a Policy Working Group have been subsumed by other entities, and noting that Patient and Public Voice (PPV) members of the National Programme Board for Gender Dysphoria Services felt unable to assure aspects of the process.**
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**SECTION 2 – IMPACT REPORT**

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| No | Item | N/Cost £K | Level of uncertainty |
| 1. | Number of patients affected in England | 0 | This is a “not for routine commissioning” policy proposition |
| 2. | Total cost per patient over 5 years | £0 |  |
| 3. | Budget impact year 1 | £0 | Puberty Suppressing Hormones (PSH) are “in-tariff” if prescribed in secondary care or included in GP Prescribing budgets if prescribed locally. |
| 4. | Budget impact year 2 | £0 | As above |
| 5. | Budget impact year 3 | £0 | As above |
| 6. | Budget impact year 4 | £0 | As above |
| 7. | Budget impact year 5 | £0 | As above |
| 8. | Total number of patients treated over 5 years | 0 |  |
| 9. | Net cost per patient treated over 5 years | £0 |  |
| Key additional information |
| Puberty Suppressing Hormones (PSH) are not funded separately as they are not excluded from tariff. Therefore any savings from the cessation of prescribing will fall to providers if prescribed in secondary care or ICBs if prescribed in primary care.The endocrine/CYP gender service is funded on a fixed cost basis, so there is also not expected to be any savings from the cost of prescribing in secondary care. |