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EXHIBIT E

WILENCHIK & BARTNESS
A PROFESSIONAL CORPORATION

MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
6th March 2024

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

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

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
Not recommended to be available as a routinely commissioned treatment option for the treatment of children and adolescents who have gender incongruence.

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

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.

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?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Impact on gender dysphoria **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria. The study measured the impact on gender dysphoria at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.**
Impact on mental health: depression	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.

Certainty of evidence: very low	One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. The study provided evidence for depression measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.**
Impact on mental health: anger **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger. The study provided evidence for anger measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.**
Impact on mental health: anxiety **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. Anxiety was measured using the Trait Anxiety Scale of the State-Trait Personality Inventory

	(STAI). This is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. The study provided evidence for anxiety at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276) (**VERY LOW**). **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.**
Quality of life	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified.
Important outcomes	
Impact on body image **Certainty of evidence: very low**	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image (de Vries et al. 2011). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study (de Vries et al. 2011) provided evidence for body image measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) body image (BIS) scores for were not statistically significantly different from baseline compared with follow-up for: • primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145) • secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569) • neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620) **(VERY LOW)**.

	This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.
Psychosocial impact: global functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. One uncontrolled, observational, prospective cohort study (de Vries et al 2011) and one prospective cross-sectional cohort study (Costa et al. 2015) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children's Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning. One study (de Vries et al. 2011) provided evidence for global functioning (CGAS) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005) **(VERY LOW)**. One study (Costa et al. 2015) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points: • at baseline (T0) in both groups, • after 6 months of psychological support in both groups (T1), • after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and • after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3). The mean [±SD] CGAS score was statistically significantly higher (improved) for all adolescents (including those not receiving GnRH analogues) at T1, T2 or T3 compared with baseline (T0). For the immediately eligible group (who received GnRH analogues) versus the delayed eligible group (who did not receive GnRH analogues) there were no statistically significant differences in CGAS scores between the 2 groups at baseline T0 (n=201, p=0.23), T1 (n=201, p=0.73), T2 (n=121, p=0.49) or T3 (n=71, p=0.14) time points. For the immediately eligible group (who received GnRH analogues), the mean (±SD) CGAS score was not statistically significantly different at:

	• T1 compared with T0 • T2 compared with T1 • T3 compared with T2. The mean (±SD) CGAS score was statistically significantly higher (improved) at: • T2 compared with T0 (n=60, 64.70 [±13.34] versus n=101, 58.72 [±11.38], p=0.003) • T3 compared with T0 (n=35, 67.40 [±13.39] versus n=101, 58.72 [±11.38], p<0.001) • T3 compared with T1 (n=35, 67.40 [±13.93] versus n=101, 60.89 [±12.17], p<0.001) **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.**
Psychosocial impact: psychosocial functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study (de Vries et al, 2011) and 1 cross-sectional observational study (Staphorsius et al. 2015) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent's age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range. One study (de Vries et al. 2011) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). At follow up, the mean (±SD) CBCL scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001 • Internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001)

	• Externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). At follow up, the mean (±SD) YSR scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001) • Internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) • Externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017) **(VERY LOW)**. One study (Staphorsius et al. 2015) assessed CBCL in a cohort of adolescents with gender dysphoria (transfemale: n=18, mean [±SD] age 15.1 [±2.4] years and transmale: n=22, mean [±SD] age 15.8 [±1.9] years) either receiving GnRH analogues (transfemale, n=8 and transmale, n=12), or not receiving GnRH analogues (transfemale, n=10 and transmale, n=10). The mean (±SD) CBCL scores for each group were (statistical analysis unclear): • transfemales (total) 57.8 [±9.2] • transfemales receiving GnRH analogues 57.4 [±9.8] • transfemales not receiving GnRH analogues 58.2 [±9.3] • transmales (total) 60.4 [±10.2] • transmales receiving GnRH analogues 57.5 [±9.4] • transmales not receiving GnRH analogues 63.9 [±10.5] **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues psychosocial functioning may improve, with the proportion of adolescents in the clinical range for some CBCL and YSR scores decreasing over time.**
Engagement with health care services **Certainty of evidence: very low**	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. Two uncontrolled observational cohort studies provided evidence relating to loss to follow up, which could be a marker of engagement with health care services (Brik et al. 2018 and Costa et al. 2015). In one retrospective study (Brik et al. 2018), 9 adolescents (9/214, 4.2%) who had stopped attending appointments were excluded from the study between November 2010 and July 2019 **(VERY LOW)**. One prospective study (Costa et al. 2015) had evidence for a large loss to follow-up over time. The sample size at baseline (T0) and 6 months (T1) was 201, which dropped by 39.8% to 121 after 12 months (T2) and by 64.7% to 71 at 18 months follow-up (T3). No explanation of the reasons for loss to follow-up are reported **(VERY LOW)**.

	Due to their design there was no reported loss to follow-up in the other 3 effectiveness studies (de Vries et al 2011; Khatchadourian et al. 2014; Staphorsius et al. 2015). **These studies provide very low certainty evidence about loss to follow up, which could be a marker of engagement with health care services, during treatment with GnRH analogues. Due to the large variation in rates between studies no conclusions could be drawn.**
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.
Stopping treatment **Certainty of evidence: very low**	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents with gender dysphoria. Two uncontrolled, retrospective, observational cohort studies provided evidence relating to stopping GnRH analogues. One study had complete reporting of the cohort (Brik et al. 2018), the other (Khatchadourian et al. 2014) had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Brik et al. 2018 narratively reported the reasons for stopping GnRH analogues in a cohort of 143 adolescents (38 transfemales and 105 transmales). Median age at the start of GnRH analogues was 15.0 years (range, 11.1–18.6 years) in transfemales and 16.1 years (range, 10.1–17.9 years) in transmales. Of these adolescents, 125 (87%, 36 transfemales, 89 transmales) subsequently started gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRH analogues. At the time of data collection, the median duration of GnRH analogue use was 2.1 years (1.6–2.8). During the follow-up period 6.3% (9/143) of adolescents had discontinued GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). The percentages and reasons for stopping were: • 2.8% (4/143) stopped GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: ○ 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues ○ 1 transmale had hot flushes, increased migraines, fear of injections, stress at school and unrelated medical issues, and temporarily stopped treatment (after 4 months) and restarted 5 months later. ○ 1 transmale had mood swings 4 months after starting GnRH analogues. After 2.2 years had unexplained severe nausea and rapid weight loss and discontinued GnRH analogues after 2.4 years ○ 1 transmale stopped GnRH analogues because of inability to regularly collect medication and attend appointments for injections. • 3.5% (5/143) stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons **(VERY LOW)**.

	Khatchadourian et al. 2014 narratively reported the reasons for stopping GnRH analogues in a cohort of 26 adolescents (15 transmales and 11 transfemales), 42% (11/26) discontinued GnRH analogues during follow-up between 1998 and 2011. Of 15 transmales receiving GnRH analogues, 14 received testosterone during the observation period, of which: • 7 continued GnRH analogues after starting testosterone • 7 stopped GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: ○ 5 stopped after hysterectomy and salpingo-oophorectomy ○ 1 stopped after 2.2 years (transitioned to gender-affirming hormones) ○ 1 stopped after <2 months due to mood and emotional lability **(VERY LOW)**. Of 11 transfemales receiving GnRH analogues, 5 received oestrogen during the observation period, of which: • 4 continued GnRH analogues after starting oestrogen • 1 stopped GnRH analogues when taking oestrogen (no reason reported) **(VERY LOW)**. Of the remaining 6 transfemales taking GnRH analogues: • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before taking oestrogen (the following year delayed due to heavy smoking) • 1 stopped GnRH analogues after 13 months due not to pursuing transition **(VERY LOW)**. **These studies provide very low certainty evidence for the number of adolescents who stop GnRH analogues and the reasons for this.**

Outcome	Evidence statement
Safety	
Change in bone density: lumbar **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in lumbar bone density. Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on lumbar BMAD) between starting with a GnRH analogue and at 1 and 2 year intervals (Joseph et al. 2019), and between starting GnRH analogues and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. It was reported as g/cm^3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of −1 is equal to 1 standard deviation below the

	mean, and a z-score of +1 is equal to 1 standard deviation above the mean. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMAD increase using z-scores. • The z-score for lumbar BMAD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score [±SD]: baseline 0.486 [0.809], 2 years −0.279 [0.930], p=0.000) and transmales (baseline −0.361 [1.439], 2 years −0.913 [1.318], p=0.001) (VERY LOW). • The z-score for lumbar BMAD was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [0.154], 1 year −0.228 [1.027], p=0.000) and transmales (baseline −0.186 [1.230], 1 year −0.541 [1.396], p=0.006) (VERY LOW). • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between baseline and 1 or 2 years in transfemales or transmales (VERY LOW). Two retrospective observational studies (Klink et al. 2015 and Vlot et al. 2017, n=104 in total) provided non-comparative evidence on change in lumbar BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klink et al. 2015 the z-score for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.28 [±0.90], gender-affirming hormone −0.50 [±0.81], p=0.004). Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales (VERY LOW). Vlot et al. 2017 reported change from starting GnRH analogues to starting gender-affirming hormones in lumbar BMAD by bone age. • The z-score for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.20 [−1.82 to 1.18], gender-affirming hormone −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years (VERY LOW). • The z-score for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.05 [−0.78 to 2.94], gender-affirming hormone −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.60 to 1.80], gender-affirming hormone −0.29 [−2.28 to 0.90], p≤0.0001) (VERY LOW). • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and

	starting gender-affirming hormones in transfemales or transmales with young or old bone age (VERY LOW). Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on lumbar BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMD increase using z-scores. • The z-score for lumbar BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.130 [0.972], 2 years −0.890 [±1.075], p=0.000) and transmales (baseline −0.715 [±1.406], 2 years −2.000 [1.384], p=0.000) (VERY LOW). • The z-score for lumbar BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline −0.016 [±1.106], 1 year −0.461 [±1.121], p=0.003) and transmales (baseline −0.395 [±1.428], 1 year −1.276 [±1.410], p=0.000) (VERY LOW). • With the exception of transmales, where lumbar BMD in kg/m^2 increased between baseline and 1 year (mean [±SD]: baseline 0.694 [±0.149], 1 year 0.718 [±0.124], p=0.006), actual lumbar BMD values were not statistically significantly different between baseline and 1 or 2 years in transfemales or between 0 and 2 years in transmales (VERY LOW). One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in lumbar BMD between starting GnRH analogues and starting gender-affirming hormones. • The z-score for lumbar BMD was not statistically significantly different between starting GnRH analogue and starting gender-affirming hormone treatment in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.17 [±1.18], gender-affirming hormone −0.72 [±0.99], p<0.001) (VERY LOW). • Actual lumbar BMD in g/cm^2 was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (mean [±SD]: GnRH analogues 0.95 [±0.12], gender-affirming hormones 0.91 [±0.10], p=0.006) (VERY LOW). **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD).**

Change in bone density: femoral **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in femoral bone density. Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on femoral BMAD) between starting treatment with a GnRH analogue and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales (VERY LOW). • Actual femoral area BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transmales or transfemales (VERY LOW). One retrospective observational study (Vlot et al. 2017, n=70) provided non-comparative evidence on change in femoral neck (hip) BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • The z-score for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.71 [−3.35 to 0.37], gender-affirming hormone −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogue −0.44 [−1.37 to 0.93], gender-affirming hormone −0.36 [−1.50 to 0.46]) (VERY LOW). • The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.39 to 1.32], gender-affirming hormone −0.27 [−1.91 to 1.29], p=0.002) (VERY LOW). • Actual femoral neck BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or in transmales with a young bone age, but were statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.33 [0.25 to 0.39), gender-affirming hormone 0.30 [0.23 to 0.41], p≤0.01) (VERY LOW). Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on

	femoral BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in femoral neck BMD increase using z-scores. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral neck BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001) (VERY LOW). • The z-score for femoral neck BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline 0.157 [±0.905], 1 year −0.340 [±0.816], p=0.002) and transmales (baseline −0.863 [±1.215], 1 year −1.440 [±1.075], p=0.000) (VERY LOW). • Actual femoral neck BMD values in kg/m^2 were not statistically significantly different between baseline and 1 or 2 years in transmales or transfemales (VERY LOW). One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower in transmales (z-score mean [±SD]: GnRH analogue 0.36 [±0.88], gender-affirming hormone −0.35 [±0.79], p=0.001) (VERY LOW). • Actual femoral area BMD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but were statistically significantly lower in transmales (mean [±SD] GnRH analogue 0.92 [±0.10], gender-affirming hormone 0.88 [±0.09], p=0.005) (VERY LOW). **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD), apart from actual femoral area BMD in transmales.**
Cognitive development or functioning **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for cognitive development and puberty suppression may affect cognitive development or functioning. One cross-sectional observational study (Staphorsius et al. 2015, n=70) provided comparative evidence on cognitive development or functioning in adolescents with gender dysphoria on GnRH analogues compared with adolescents with gender dysphoria not on GnRH

	analogues. Cognitive functioning was measured using an IQ test. Reaction time (in seconds) and accuracy (percentage of correct trials) were measured using the Tower of London (ToL) task. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. No statistical analyses or interpretation of the results in these groups were reported: • IQ in transfemales (mean [±SD] GnRH analogue 94.0 [±10.3], control 109.4 [±21.2]). IQ transmales (GnRH analogue 95.8 [±15.6], control 98.5 [±15.9]. • Reaction time in transfemales (mean [±SD] GnRH analogue 10.9 [±4.1], control: 9.9 [±3.1]). Reaction time transmales (GnRH analogue 9.9 [±3.1], control 10.0 [±2.0]). • Accuracy score in transfemales (GnRH analogue 73.9 [±9.1], control 83.4 [±9.5]. Accuracy score in transmales (GnRH analogue 85.7 [±10.5], control 88.8 [±9.7]. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning. No conclusions could be drawn.**
Other safety outcomes: kidney function **Certainty of evidence: very low**	This is an important outcome because if renal damage (raised serum creatinine is a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on change in serum creatinine between starting GnRH analogues and at 1 year. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • There was no statistically significant difference between baseline and 1 year for serum creatinine in transfemales (mean [±SD] baseline 70 [±12], 1 year 66 [±13], p=0.20). • There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [±8], 1 year 68 [±13], p=0.01). **This study provides very low certainty evidence that GnRH analogues do not affect renal function.**
Other safety outcomes: liver function **Certainty of evidence: very low**	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on elevated liver enzymes between starting GnRH analogues and during use. No comparative values or statistical analyses were reported. • Glutamyl transferase was not elevated at baseline or during use in any person. • Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during use than at baseline. • Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of use.

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

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

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?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. The mean (±SD) UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean UGDS score [±SD]: 47.95 [±9.70] versus 56.57 [±3.89]) and T1 (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001 **(VERY LOW)**.

	One further prospective observational longitudinal study (Costa et al. 2015) provided evidence for the impact on gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. Sex assigned at birth males had a statistically significantly lower (improved) mean (±SD) UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001). However, it was not reported if this was baseline or follow-up **(VERY LOW)**. **These studies provide very low certainty evidence that in sex assigned at birth males (transfemales), gender dysphoria is lower than in sex assigned at birth females (transmales).** **Impact on mental health** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for the impact on mental health (depression, anger and anxiety) in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. • The mean (±SD) depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and T1 (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057 • The mean (±SD) anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean TPI score [±SD]: 5.22 [±2.76] versus 6.43 [±2.78]) and T1 (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022 • The mean (±SD) anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and T1 (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001 **(VERY LOW)**. **This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression. However, sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at both baseline and follow up.** **Impact on body image** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth males. • The mean (±SD) BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at

	both baseline (T0) (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and T1 (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]), between sex difference p=0.047 • The mean (±SD) BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and T1 (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001 • The mean (±SD) BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.60 [±0.58] versus 2.24 [±0.62]) and T1 (n=not reported, 2.32 [±0.59] versus 2.61 [±0.50]), between sex difference p=0.777 **(VERY LOW)**. **This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.** **Psychosocial impact** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth males. • Sex assigned at birth males had statistically higher mean (±SD) CGAS scores compared with sex assigned at birth females at both baseline (T0) (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and T1 (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL Total T score at T0 or T1 (n=54, p=0.110) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL internalising T score at T0 or T1 (n=54, p=0.286) • Sex assigned at birth males had statistically lower mean (±SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and T1 (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR Total T score at T0 or T1 (n=54, p=0.164) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR internalising T score at T0 or T1 (n=54, p=0.825) • Sex assigned at birth males had statistically lower mean (±SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [±11.38] versus 57.24

[±10.59]) and T1 (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004 **(VERY LOW)**.

One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth males.

- Sex assigned at birth males had statistically significant lower mean (±SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03) **(VERY LOW)**.

These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). However, no conclusions could be drawn.

Change in bone density: lumbar
Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results.

These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales).

Change in bone density: femoral
Three uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on femoral bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results.

These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth males (transfemales).

Cognitive development or functioning
One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth males. See the safety results table above for a full description of the results.

This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on

	cognitive development or functioning in sex assigned at birth males (transfemales). No conclusions could be drawn. **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth males (transfemales).**
Sex assigned at birth females (transmales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) and one prospective observational longitudinal study (Costa et al. 2015) provided evidence for gender dysphoria in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that in sex assigned at birth females (transmales), gender dysphoria is higher than in sex assigned at birth males (transfemales) at both baseline and follow up.** **Impact on mental health** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on mental health (depression, anger and anxiety) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression. However, sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at baseline and follow up.** **Impact on body image** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics**

	than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different. **Psychosocial impact** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth females. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales).** **Change in bone density: femoral** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on femoral bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth females (transmales), apart from actual femoral area.** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth females. See the safety results table above for a full description of the results.

	This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth females (transmales). No conclusions could be drawn. **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth females (transmales). See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth females (transmales).**
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at which GnRH analogue started	No evidence was identified.
Age at onset of puberty	No evidence was identified.
Tanner stage at which GnRH analogue started	No evidence was identified.
Diagnosis of autistic spectrum disorder	No evidence was identified.
Diagnosis of mental health condition	No evidence was identified.

Considerations from review by Rare Disease Advisory Group
Not applicable

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.

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.**

SECTION 2 – IMPACT REPORT

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.			

EXHIBIT F

WILENCHIK & BARTNESS
A PROFESSIONAL CORPORATION

NHS England: Equality and Health Inequalities Impact Assessment (EHIA)

A completed copy of this form must be provided to the decision-makers in relation to your proposal. The decision-makers must consider the results of this assessment when they make their decision about your proposal.

1 March 2024 (amended following public consultation)

1. Name of the proposal: Gender Incongruence Service for Children and Young People: Prescribing Gonadotrophin Releasing Hormone Analogues (Puberty Suppressing Hormones)

2. Brief summary of the proposal

NHS England proposes that Gonadotrophin Releasing Hormone analogues (GnRHa) are not recommended to be available as a routine commissioning option for treatment of children and adolescents who have gender incongruence. GnRHa are commonly referred to as 'puberty blockers' or puberty suppressing hormones.

What is GnRHa?

Administration of GnRHa initially produces an initial phase of stimulation of hormone receptors; continued administration leads to down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production (NICE: British National Formulary for Children). GnRHa are currently prescribed through the NHS for children and young people with a diagnosis of persistent gender dysphoria from Tanner Stage 2 of pubertal development, alongside psychosocial and psychological support, though no formal clinical commissioning policy is in place.

Who will be impacted by the policy?

Children and young people aged between around 10 and 17 years – this will be a combination of a prospective cohort (i.e. future referrals to an NHS commissioned specialised gender incongruence service); and those currently in the service and not yet onwardly referred to an endocrine clinic.

For children and young people who, at the point the clinical commissioning policy takes effect on 1 April 2024:

- have been referred into an endocrine clinic by the former NHS Gender Identity Development Service but have not yet been assessed by a consultant endocrinologist for suitability of GnRHa; or
- are under the clinical care of an endocrine team at University College of London Hospitals NHS Foundation Trust or Leeds Teaching Hospitals NHS Trust following a referral by the former NHS Gender Identity Development Service

there is an expectation that GnRHa will continue to be administered / be initiated, if that is the informed choice of the young person / parents of a child under 16 years[1], subject to the outcome of usual clinical review of the individual's existing individual care plan jointly between the individual's Lead Clinician and the young person / parents of a child under 16 years.

What may be the impacts of the policy?
The direct impact will be that for children and young people who are assessed and diagnosed with gender incongruence by an NHS commissioned Children and Young People's Gender Service, GnRHa would no longer be routinely commissioned as a clinical intervention on the NHS-commissioned pathway of care. Although adoption of the policy is not contingent on the formation of a clinical study, some children may be eligible for enrolment in a research framework that would provide access to GnRHa, while some young people may not be eligible (see below). The development of a research protocol is well underway and will be subject to the usual approvals through the National Institute for Health and Care Research. NHS clinicians within the Children and Young People's Gender Service would no longer prescribe GnRHa for children and young people as a response to gender incongruence or gender dysphoria outside of a research framework, should a research framework be feasible. The direct consequence of the policy is that some children and young people who may otherwise have been prescribed GnRHa and who are not eligible to join such a research framework or those who are eligible but who opt to not enrol in the research framework, will proceed with pubertal progression and development of secondary sexual characteristics of the natal sex. If the establishment of a research framework is not, in fact, feasible then no child or young person will be prescribed GnRHa as a response to gender incongruence / dysphoria.

Potential consequences of the policy may be an increase in the number of children and young people who seek GnRHa from unregulated sources; and some stakeholder groups have previously suggested[2] that withholding GnRHa will lead to an increase in emotional and psychological distress, leading to risk-taking behaviour particularly amongst adolescents. Conversely, some stakeholder groups have

[1] NHS England's adoption of the proposal would not be intended to compel young people / parents of children under 16 years to choose to continue with GnRHa if, after a consideration of the issues raised by the adoption of the policy, they make a decision to cease the intervention.

[2] Around 2020/21, when the Tavistock and Portman NHS Foundation Trust took the decision to cease making referrals to endocrine clinics in response to a legal ruling (referrals resumed in 2021 following judgment of the Court of Appeal).

suggested[3] that GnRHa should be removed from the NHS pathway of care completely in the best interests of children and young people in view of the limited evidence around treatment aims, benefits, risks and outcomes[4].

If the policy is adopted by NHS England following public consultation, it would be appropriate to make a consequential change to the related clinical policy for prescribing cross-sex hormones for young people with gender dysphoria.

How does the policy relate to the recommendation of the Cass Review that a research framework should be established?

In 2022 the independent Cass Review advised that consideration be given to the rapid establishment of the necessary research infrastructure to prospectively enrol young people being considered for GnRHa into a formal research programme with adequate follow up into adulthood[5].

> "*My interim report highlighted the gaps in the evidence base regarding all aspects of gender care for children and young people from epidemiology through to assessment, diagnosis, support, counselling and treatment. NHS England asked me to give some further thought as to how these gaps may be addressed…. Given the particular uncertainties regarding long-term outcomes of medical intervention, and the broader knowledge gaps in this area, there is an imperative to build research capacity into the national network …. A further concern is that adolescent sex hormone surges may trigger the opening of a critical period for experience-dependent rewiring of neural circuits underlying executive function (i.e. maturation of the part of the brain concerned with planning, decision making and judgement). If this is the case, brain maturation may be temporarily or permanently disrupted by puberty blockers, which could have significant impact on the ability to make complex risk-laden decisions, as well as possible longer-term neuropsychological consequences. To date, there has been very limited research on the short-, medium- or longer-term impact of puberty blockers on neurocognitive development. In light of these critically important unanswered questions, I would suggest that consideration is given to the rapid establishment of the necessary research infrastructure to prospectively enrol young people being considered for hormone treatment into a formal research programme with adequate follow up into adulthood, with a more immediate focus on the questions regarding puberty blockers*".

NHS England accepted that advice and incorporated wording to that effect in the proposed interim service specification for children and young people's gender incongruence services that was agreed in 2023 following a process of public consultation. NHS England has now established a National Research Oversight Board for Children and Young People's Gender Services. Membership includes the National

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[3] Responses to NHSE public consultation on proposed interim service specification for services for children and young people with gender dysphoria
[4] Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria; National Institute for Health and Care Excellence, 2020
[5] Letter to NHS England, 19 July 2022

Institute for Health and Care Research, the Medical Research Council, the Royal College of Paediatrics and Child Health and a range of other clinical and academic experts. The National Research Oversight Board has approved the development of a study into the impact of GnRHa on gender incongruence in children and young people with early-onset gender dysphoria. The study design and feasibility assessment is being taken forward through the National Research Collaboration Programme in place between NHS England and NIHR, with the study team planning to engage with stakeholders in the study design. Subject to the usual ethical and scientific approvals, NHS England anticipates that recruitment to the study will open in 2024.

Alongside this first proposed study, further engagement is also planned to identify the key evidence gaps for children and young people with later-onset gender dysphoria – recognising that there is even greater uncertainty in terms of the supporting clinical evidence base, less established clinical practice and less known about the natural history of gender incongruence / dysphoria in this group.

The definition of 'early onset' and 'late onset' will be developed by the clinical study team in due course.

In summary, the impacts of the proposed policy in terms of access to GnRHa are likely to be:

- Children and young people with gender incongruence / dysphoria will not be referred for consideration of GnRHa unless and until the proposed puberty suppressing hormone study opens to recruitment
- As an outcome of public consultation NHS England has removed the proposed 'exceptional circumstances' pathway that, if adopted, may have granted some individuals access to GnRHa outside of a clinical study
- Should the study open to recruitment, only children presenting with early-onset gender dysphoria (yet to be defined), and who meet any other key study entry criteria, will be able to enrol in the study
- Young people with later-onset gender dysphoria (yet to be defined) would not be eligible for referral for GnRHa; further consideration is being given to how best to work with a range of stakeholders to identify and articulate the material evidence gaps, and how to gather further evidence, to support future options for young people with later-onset gender dysphoria
- Should the proposed study not be granted the usual approvals, no child or young person receiving care for gender incongruence / dysphoria would be eligible for GnRHa
- Adoption of the policy is not planned to impact children and young people who were referred into an NHS-commissioned paediatric endocrinology service before 1 April 2024, and other patient groups such as children receiving GnRHa for Central Precocious Puberty
- The administration of GnRHa to natal males as part of a Gender Affirming Hormone intervention is intended to achieve a different clinical outcome, in that Gender Affirming Hormone treatment via physiologic doses of oestrogen alone is insufficient to suppress testosterone levels into the normal range for natal females and addition of an anti-androgen is necessary. The use of an anti-androgen will continue to be available for this purpose in natal males, not before middle adolescence, who are prescribed Gender

Affirming Hormones from around 16 years of age[6], and for natal males who are aged 17 years and above who are seen by adult Gender Dysphoria Clinics.

3. Prevalence

Estimates for the proportion of children, young people and adults with gender incongruence or gender dysphoria vary considera bly. This reflects a number of factors such as: variable data reporting by providers; differences in diagnostic thresholds applied and inconsistent terminology; the methodology and diagnostic classification used – population surveys give a much higher estimate than numbers based on service use; and the year and country in which the studies took place. Few studies have taken place in the United Kingdom, and there are no published studies in young children.

The UK census (2021) reported that 93.47% of respondents in England (16 years +) recorded a "*gender identity the same as sex registered at birth*"; and that 0.55% of respondents recorded a "*gender identity different from sex registered at birth";* and that 5.98% of respondents recorded as '*not answered"*[7]*.* Although the Official for National Statistics advises (November 2023) that "*the census estimates on gender identity are broadly consistent with the best available comparator of the GP Patent Survey and international comparators*" the UK census did not collect gender identity data for children below 16 years of age.

Published estimates for the proportion of people who are gender diverse range from 0.3% to 0.5% of adults, and around 1.2% of people aged 14-18 years (source: analysis by Public Health Consultant, NHS England, 2023). The number of referrals to specialised gender incongruence services for children and young people in England is currently likely to be around 1 per 2000 population per yea r. The current referral profile suggests that the majority of referrals will be of adolescents following the onset of puberty.

Table: Patient Numbers (updated February 2024)

[6] See NHS England's Clinical Commissioning Policy "Prescribing Gender Affirming Hormones as Part of the Children and Young Peop le's Gender Service", as amended 2024. The Independent Cass Review advised NHS England in July 2022 that there should be "a more immediate focus on the questions regarding puberty blockers", and NHS England has proceeded to follow this advice in regard to GnRHa when used for the purpose of puberty suppression separate to the administration of gender affirming hormones.

[7] The Office for National Statistics advises (November 2023) that "*there are some patterns in the data that are consistent with, but do not conclusively demonstrate, some respondents not interpreting the question [on gender identity] as intended; given other courses of uncertainty, not leas t the impact of question of non-response, we cannot say with certainty whether the census estimates are more likely to be an overestimate or an underestimate of the total number of trans people aged over 16 years in England and Wales*".

Patient Cohort	Number	Commentary
Number of children under 16 years of age who are likely to be directly impacted by the policy at current referral patterns.	5 per month	Average figure - data from independent Multi-Professional Review Group is that between 10 August 2021 and 26 January 2024 the Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust referred 137 children under 16 years to an endocrine clinic for assessment of suitability for GnRHa. However, clinical activity at the GIDS has steadily decreased in recent years due to staff attrition. Up to 2021 the Tavistock reported that around 15 – 20% of children and young people seen by GIDS were referred to an endocrine clinic and that 2545 patients were referred to an endocrine clinic in 2019/20 (including young people aged 16 years and over). NHS England does not hold data that would differentiate between individuals who present with early-onset gender dysphoria and those who present with late-onset gender dysphoria – and the clinical study team has yet to define these terms.
Number of CYP who may be referred to an endocrine clinic per year under a new configuration of service providers, based on 2019/20 referral rate (before the judgment of Bell and Mrs A v Tavistock and Portman NHS Foundation Trust)	32 – 42 per month	As above – up to 2021 the Tavistock and Portman NHS Foundation Trust reported that around 15 – 20% of children and young people seen by GIDS were referred to an endocrine clinic and that 2545 patients were referred to an endocrine clinic in 2019/20 (including young people aged 16 years and over).

Number of patients under 16 years currently on the waiting list for GIDS, who may be impacted by policy	462 - 616	There were 3,423 children under 16 years on the waiting list held by *NHS AGEM Commissioning Support Unit* as at 31 December 2023 (source: AGEM CSU); assume 90% of those are the commissioning responsibility of NHSE; of those, Tavistock and Portman NHS FT reports that around 15-20% would be referred to endocrine clinic at historical referral rates NHS England does not hold data that would differentiate between individuals who present with early-onset gender dysphoria and those who present with late-onset gender dysphoria - and the clinical study team has yet to define these terms.
Number of patients aged 16 and 17 years currently on the waiting list for GIDS, who may be impacted by policy	315 - 420	There were 2,336 young people aged 16 and above on the waiting list held by *NHS AGEM Commissioning Support Unit* as at 31 December 2023 (source: AGEM CSU); assume 90% of those are the commissioning responsibility of NHSE; of those, Tavistock and Portman NHS FT reports that around 15-20% would be referred to endocrine clinic at historical referral rates. *Note: these figures do not reflect the number of young people on the waiting list who will not be seen by GIDS by the time of their 18th birthday and / or who may be referred to an adult Gender Dysphoria Clinic from 17 years of age.* NHS England does not hold data that would differentiate between individuals who present with early-onset gender dysphoria and those who present with late-onset gender dysphoria - and the clinical study team has yet to define these terms.

Number of children and young people who will be receiving GnRHa for the purpose of puberty suppression from an NHS endocrine team on 31 March 2024; or who will be waiting for assessment by the endocrine team.	<71	Source: Planning assumptions provided by Tavistock and Portman NHS Foundation Trust on 27 February 2024.

4. Main potential positive or adverse impact of the proposal for protected characteristic groups summarised

Please briefly summarise the main potential impact (positive or negative) on people with the nine protected characteristics (as listed below). Please state **N/A if your proposal will not impact adversely or positively on the protected characteristic groups listed below. Please note that these groups may also experience health inequalities.**

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
Age: older people; middle years; early years; children and young people.	The impact of the policy would be that GnRHa will not be routinely available through the NHS (for individuals with gender incongruence) for individuals who share the protected characteristic of 'age' as it would only impact individuals aged between (around) 10 years and 17 years. The policy is not likely to impact children below the age of 10 years given that recommendations for GnRHa have not been made by the GIDS at the Tavistock and Portman NHS Foundation Trust until the child has reached Tanner Stage 2 of pubertal development (*source: NHS Service Specification for Gender Identity Development Service, 2016*).	Other forms of specialist clinical support will remain available through the NHS for this patient cohort; the NHS England interim service specification for gender incongruence (June 2023) describes a multi-disciplinary approach to care that focuses on psychoeducation, psychosocial and psychological approaches, and aims to reduce distress and promote wellbeing and functioning. The interim service specification also describes a more coordinated and integrated approach between the specialist service and local services in the child or young person's best interests. NHS England is leading a national transformation programme that plans to significantly increase clinical capacity in children and young people's gender incongruence services over time – thereby increasing more timely service provision.

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	As part of the planning for the closure of GIDS the Tavistock and Portman NHSFT has advised NHS England (November 2023) that over fifty percent of referrals made by the Tavistock for GnRHa are of children under 16 years of age. Should the proposed clinical study be established (anticipated 2024) children and young people with later on-set gender dysphoria will not be eligible for the study, though the study team has yet to define this term. <u>GnRHa alongside Gender Affirming Hormones for Natal Males</u> The administration of GnRHa to natal males as part of a Gender Affirming Hormone intervention is intended to achieve a different clinical outcome, in that Gender Affirming Hormone treatment via physiologic doses of oestrogen alone is insufficient to suppress testosterone levels into the normal range for natal females and addition of an anti-androgen is necessary. The use of an anti-androgen will continue to be available for this purpose in natal males, not before middle adolescence, who are prescribed Gender Affirming Hormones from around 16 years of age, and for natal males who are aged 17	As a risk mitigation measure, in April 2024 NHS England will have commissioned a rapid assessment service for every child or young person on the waiting list for CYP Gender Services, through local NHS children and young people's mental health services. This will be a directly commissioned service for this cohort over-and-above existing mental health provision. *Criteria for enrolment in a clinical study* Alongside the first proposed study, further engagement is also planned by the National Research Oversight Board to identify the key evidence gaps for children and young people with later-onset gender dysphoria (yet to be defined) – recognising that there is even greater uncertainty in terms of the supporting clinical evidence base, less established clinical practice and less known about the natural history of gender dysphoria in this group. The clinical study team has yet to define these terms.

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	years and above who are seen by adult Gender Dysphoria Clinics. NHSE has concluded that the fact that the policy will mainly impact children and young people who share the protected characteristic of "age" does not result in unlawful discrimination. The policy is a reasonable, rational and clinically necessary response to the findings of NICE and the Cass Review that there is a lack of sufficient evidence relating to the safety and clinical effectiveness of GnRHa for children and young people with gender incongruence / dysphoria, including about the benefits, risks and long-term outcomes. It is therefore proposed that adoption of the policy would in itself be a risk mitigation measure.	
Disability: physical, sensory and learning impairment; mental health condition; long-term conditions.	Various literature suggests that a high proportion of children and young people with gender incongruence / dysphoria will also present with other significant comorbidities, though NHSE does not have specific data from the GIDS at the Tavistock and Portman NHS Foundation Trust nor from the commissioned endocrine clinics on the number of children and young people open to the GIDS who have a disability.	Other forms of specialist clinical support will remain available through the NHS for this patient cohort; the NHS England interim service specification for gender incongruence (June 2023) describes a multi-disciplinary approach to care that focuses on psychosocial and psychological approaches, and psychoeducation. The interim service specification also describes a more coordinated and integrated approach between the specialist service and local services

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	The literature reports that a significant proportion of those presenting with gender dysphoria have a diagnosis of Autistic Spectrum Disorder (ASD). Around 35% of young people referred to the NHS-commissioned children and young people's service present with moderate to severe autistic traits[8]. Individuals with ASD are likely to share the protected characteristic of "disability". Around 70% of people with autism also meet diagnostic criteria for at least one (often unrecognised) psychiatric disorder that further impairs psychosocial functioning, for example, attention deficit hyperactivity disorder or anxiety disorders. Intellectual disability (IQ<70) coexists in approximately 50% of children and young people with autism[9]. There is also an increased prevalence of children and young people presenting to the current service with severe forms of mental health problems which may in some cases constitute a 'disability' for the purpose of the Act[10].	in the child or young person's best interests including where the child or young person has complex co-presentations that may form the basis of a 'disability' under the Equality Act including autism, ADHD, other forms of neuro-disability and mental health problems. NHS England is leading a national transformation programme that plans to significantly increase clinical capacity in children and young people's gender incongruence services – thereby increasing more timely service provision and greater integration with and support from local services. The new service offer will be accompanied by improved guidance and *MindEd* psycho-education resources on gender incongruence in childhood and adolescence for local services and professionals that NHS England commissioned through (the former) Health Education England (published in 2023). These new support materials will mitigate the potential impact for children and young people becoming more entrenched in their

[8] Assessment and support of children and adolescents with gender dysphoria, Butler et al, 2018
[9] Autism Spectrum Disorder in Under 19s: Support and Management, National Institute for Health and Care Excellence, 2021
[10] A 2024 paper found that the probability of self-reporting a long-term mental health condition was higher in transgender populations, though this was self-reported data by individuals aged 16 years and above. *Watkinson; Gender-Related Self-Reported Mental Health Inequalities in Primary Care in England: A Cross-Sectional Analysis Using the GP Patient Survey, 2024*

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	The UK Government's LGBT Survey (2017) reported that 32.5% of respondents from the transgender and non-binary population self-identified as having a disability (respondents were aged 16 years and above). NHSE concludes from the information above that the current policy may have a disproportionate impact on individuals who share this protected characteristic. NHS England has concluded that no direct or indirect discrimination arises. The policy is a reasonable, rational and clinically necessary response to the findings of NICE and the Cass Review that there is a lack of sufficient evidence relating to the safety and clinical effectiveness of PSH for children and young people with gender incongruence / dysphoria, including about the benefits, risks and long-term outcomes. It is therefore proposed that adoption of the policy would in itself be a risk mitigation measure.	ill health because their expectation of receiving GnRHa has been denied. NHS England also proposes to provide specialist consultation advice and liaison for local services and professionals to provide early indirect support for families who are newly identified with gender concerns by local services and professionals. At a local level NHS England, with local commissioners, has improved 24/7 crisis helplines and crisis response services. These are also supported by training resources for crisis practitioners, especially A&E staff which will include specific LGBTQIA+ training resources developed by young people with lived experience. NHS England has also published (April 2023) a new National Framework to Deliver Improved Outcomes in All-Ages Autism Assessment Pathways: Guidance for Integrated Care Boards. This will improve access to assessments and mitigate the impact of undiagnosed autism on some children and young people's experiences. As a risk mitigation measure, in April 2024 NHS England will have commissioned a rapid assessment service for every child or young person on the waiting list for CYP Gender Services, through local NHS children and young

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
		people's mental health services. This will be a directly commissioned service for this cohort over-and-above existing mental health provision.
Gender Reassignment	In considering the application of Equality Act 2010, section 7, to this service, the High Court in R (AA) v NHS Commissioning Board (2023). found that not every child or young person referred to a specialised gender incongruence service will have the protected characteristic of gender reassignment. The Court held that children and young people who are referred to such a service do not – at the point of referral or while they remain on the waiting list - share the protected characteristic of 'gender reassignment' as a class or cohort of patients. The whole cohort of patients cannot be treated as "proposing to undergo" a process (or part of a process) for the "purpose of reassigning" their sex "by changing physiological or other attributes of sex" as a class. However, as the Court found and as NHS England accepts, many children and young people in this position will, individually, have the protected characteristic of gender re-assignment at this stage although determining that will involve a case-specific factual assessment.	Other forms of specialist clinical support will remain available through the NHS for this patient cohort; the NHS England interim service specification for gender incongruence (April 2023) describes a multi-disciplinary approach to care that focuses on psychoeducation, psychosocial and psychological approaches. The interim service specification also describes a more coordinated and integrated approach between the specialist service and local services in the child or young person's best interests. NHS England is leading a national transformation programme that plans to significantly increase clinical capacity in children and young people's gender incongruence services – thereby increasing more timely service provision. NHS England's policy will be accompanied by improved *MindEd* guidance and psycho-education resources for local services and professionals which will mitigate the potential impact for children and young people becoming more entrenched in their ill health because their expectation of receiving GnRHa has been denied. These

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	It is for this reason that NHS England has determined to treat <u>all</u> of the children and young people who will be impacted by the policy as likely to share the protected characteristic of gender reassignment, and it has proceeded on that basis throughout the whole process of policy formation. In forming the conclusion that all children and young people impacted by the policy "are likely" to share the protected characteristic of gender reassignment, NHS England has been mindful of the conflicting evidence in this regard. On the one hand, the Tavistock and Portman NHS Foundation Trust has described the purpose of GnRHa as providing time to the child or young person to help determine *whether* to pursue a process of sex reassignment[11], and on the other hand there is evidence that nearly all children and young people who received GnRHa from the Tavistock GIDS subsequently received masculinising / feminising hormones from around age 16 years[12]. <u>Impacts and Consequences</u>	resources include specific advice to primary and secondary care professionals in respect of co-existing concerns including self-harm. NHS England also proposes to provide specialist consultation advice and liaison for local services and professionals to provide early indirect support for families who are newly identified with gender concerns by local services and professionals. At a local level NHS England with local commissioners has improved 24/7 crisis helplines and crisis response services. These are also supported by training resources for crisis practitioners, especially A&E staff which will include specific LGBTQIA+ training resources developed by young people with lived experience. As a risk mitigation measure, in April 2024 NHS England will have commissioned a rapid assessment service for every child or young person on the waiting list for CYP Gender Services, through local NHS children and young people's mental health services. This will be a directly commissioned service for this cohort over-and-above existing mental health provision.

[11] Bell and Mrs A v Tavistock and Portman NHS Foundation Trust, 2020
[12] Ibid

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	GnRHA would no longer be a routinely commissioned intervention for children and young people who have this protected characteristic. Some children and young people will not be eligible to enrol in the proposed clinical study (those with later-onset gender dysphoria though this term has yet to be defined by the study team) and some who are eligible (early-onset gender dysphoria, though this term is yet to be defined by the study team) may opt to not enrol or may not meet the criteria for access that will be developed by the clinical study team in due course. Also, enrolment in a study may prove to not be an option for any child or young person, regardless of their wishes and treatment objectives, if the study does not receive the usual approvals or is otherwise deemed to be not feasible. The consequences of the policy may be an increase in the number of children and young people with this protected characteristic who seek GnRHa from unregulated sources; some stakeholder groups suggest that restrictions on gender affirming interventions may lead to an increase in risk-taking behaviour particularly amongst adolescents. Other stakeholders suggest that the policy	NHS England strongly discourages children and young people sourcing GnRHa from unregulated sources or on-line providers that are not regulated by UK regulatory bodies. The approach by NHS clinicians to children and young people who source such pharmaceuticals is described in the interim service specification for gender incongruence services. NHS England has commissioned Health Education England to deliver on-line MindEd resources directed at parents and local professionals, and these will provide improved psycho-educational

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	will have positive impacts given the limited evidence around aims, benefits, risks and outcomes. NHS England has concluded that no direct discrimination occurs. NHS England has also concluded that no indirect discrimination arises by virtue of the fact that the policy will exclusively impact individuals who share this protected characteristic. The fact that a policy will exclusively impact a specific group does not, in itself, render the policy discriminatory. The policy is a reasonable, rational and clinically necessary response to the findings of NICE and the Cass Review that a key limitation to identifying the effectiveness and safety of GnRHa in regard to children and young people with gender incongruence is the lack of reliable comparative studies. <u>Children and Young People with Gender Dysphoria who Continue on GnRHa Through an NHS Prescription Within an Existing Agreed Individual Care Plan</u> Consideration must also be given as to whether direct or indirect discrimination arises in regard to individuals who share this	advice to mitigate the need for and will caution about accessing GnRHa from unregulated sources (published in 2023). Greater involvement by and closer working between local secondary health services (CYPMHS and community child health and paediatrics) with specialist service consultation advice and liaison will further mitigate this potential impact. As a risk mitigation measure, in April 2024 NHS England will have commissioned a rapid assessment service for every child or young person on the waiting list for CYP Gender Services, through local NHS children and young people's mental health services. This will be a directly commissioned service for this cohort over-and-above existing mental health provision. *Criteria for enrolment in a clinical study* Alongside the first proposed study, further engagement is also planned by the National Research Oversight Board to identify the key evidence gaps for children and young people with later-onset gender dysphoria – recognising that there is even greater uncertainty in terms of the supporting clinical evidence base, less established clinical practice and less known about the natural history of gender dysphoria in this group. The clinical study team has yet to define these terms.

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	protected characteristic, as adoption of the policy is not planned to impact children and young people who, at the point the clinical commissioning policy takes effect have been referred into an endocrine clinic by the former NHS Gender Identity Development Service but have not yet been assessed by a consultant endocrinologist for suitability of GnRHa; or are under the clinical care of an endocrine team at University College of London Hospitals NHS Foundation Trust or Leeds Teaching Hospitals NHS Trust following a referrals by the former NHS Gender Identity Development Service. This group will share the protected characteristic of 'gender reassignment' as a class or cohort. As at January 2024 there were circa 340 children and young people under the clinical care of the endocrine team at UCLH NHSFT or Leeds Teaching Hospitals NHST, of whom around 70 are forecast to be receiving GnRHa on 31 March 2024 for the purpose of puberty suppression. NHS England has considered whether the policy for non-routine commissioning should also apply to children and young people within this group, on the basis that GnRHa	

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	should be withheld or withdrawn because of the same concerns about the lack of evidence around aims, benefits, risks and outcomes. However, there are additional ethical and clinical considerations in cases where there is an existing expectation of consideration for treatment / continued treatment[13]. This is particularly so in regard to the withdrawal of GnRHa in young people who will experience emergence or re-emergence of secondary sexual characteristics of the natal sex and who may have presented in public throughout adolescence with their suppression. On balance, NHS England has concluded that the scope of the proposed Non-Routine Commissioning Policy will not extend to children and young people in this group, subject to the outcome of usual clinical review of the individual's existing individual care plan jointly between the individual's Lead Clinician and the young person / parents of a child under 16 years. NHS England has concluded that no direct discrimination occurs.	

[13] There are similar precedents in the NHS. For example, NICE may exclude patients already being prescribed a drug from the scope of a decision that a drug should no longer be routinely available through the NHS, though these decisions are also influenced by the cost-effectiveness of the drug as assessed by NICE rather than based solely on safety grounds.

Protected characteristic groups	Summary explanation of the main potential positive or adverse impact of your proposal	Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact
	NHS England has also concluded that no indirect discrimination arises by virtue of the fact that GnRHa will continue to be routinely commissioned for this group. The policy is a reasonable, rational and clinically necessary response to the findings of NICE and the Cass Review that there is a lack of sufficient evidence relating to the safety and clinical effectiveness of PSH for children and young people with gender incongruence / dysphoria, including about the benefits, risks and long-term outcomes - and there are additional ethical and clinical considerations in regard to individuals in the proposed group who will not be subject to the policy that are distinct to those relating to individuals who will be directly impacted by the policy. NHS England's findings in this regard do not compel young people / parents of children under 16 years to choose to continue with GnRHa if, after a consideration of the issues raised by the adoption of the policy, they make a decision to cease the intervention. <u>Impact on Later Surgery</u> Some respondents to consultation objected to the statement that the potential impacts of the policy would be alleviated by other	

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	modes of specialist clinical support being made available, and that no acknowledgement had been given to the long term impacts to individuals experiencing irreversible change which could then only be corrected by surgery as an adult (for example, breast development, Adam's apple development, deepening of voice, thickening of jawline). The point was further made that facial feminisation and tracheal shave surgeries are unavailable on the NHS – and that this ought to be acknowledged in the EHIA in relation to people on a low income. The point being made here illustrates the difficulties about describing the aims and intended results of GnRHa – and the uncertainty about the aims and intended results of GnRHa highlights the difficulties in measuring the long-term impacts to individuals for the purpose of the EHIA. While some regard the rationale for prescription as being an initial part of a transition pathway, others regard it as a 'pause' to allow more time for decision making - with a decision not to pursue a transition pathway being a potential outcome.	

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	It is helpful to set out in detail the advice of the independent Cass Review in this regard: *For those who will go on to have a stable binary trans identity, the ability to pass in later life is paramount, and many will decide that the trade-offs of medical treatment are a price that is fully justified by the ability to live confidently and comfortably in their identified gender.* *The widely understood challenge is in determining when a point of certainty about gender identity is reached in an adolescent who is in a state of developmental maturation, identity development and flux.* *It is the latter option regarding a 'pause' for decision making about which we have the least information. The rationale for use of puberty blockers at Tanner Stage 2 of development was based on data that demonstrated that children, particularly birth registered boys who had early gender incongruence, were unlikely to desist once they reached early puberty; this rationale does not*	

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	necessarily apply to later presenting young people, including the predominant referral group of birth-registered girls. *We do not fully understand the role of adolescent sex hormones in driving the development of both sexuality and gender identity through the early teen years, so by extension we cannot be sure about the impact of stopping these hormone surges on psychosexual and gender maturation. We therefore have no way of knowing whether, rather than buying time to make a decision, puberty blockers may disrupt that decision-making process*". Additionally, in order to determine whether the withholding of GnRHa in adolescence leads to later surgery, NHS England would need data and evidence on the incidence of individuals who receive GnRHa in adolescence and who nonetheless choose to undergo surgical interventions in adulthood to ablate secondary sexual characteristics such as breasts or thyroid cartilage. However, NICE was unable to identify any evidence about the impact of GnRHa on the	

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	extent of later surgery (NICE evidence review, 2020) – and no material evidence was offered by respondents to consultation. In conclusion: • There is no available evidence about the long-term impacts of GnRHa in regard to the extent of later surgery • NHS England notes the advice of Dr Cass - that some individuals will decide that the risks of taking GnRHa are justified - and NHS England accepts that these individuals may share the view that adoption of the proposed policy may have a detrimental impact in regard to later surgery • But NHS England also notes Dr Cass' advice that there are uncertainties about the intended results, outcomes and effects of GnRHa (and this was also the conclusion of the NICE evidence review) • NHS England has concluded that no direct or indirect discrimination arises for these reasons <u>GnRHa alongside Gender Affirming Hormones for Natal Males</u>	

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	The administration of GnRHa to natal males as part of a Gender Affirming Hormone intervention is intended to achieve a different clinical outcome, in that Gender Affirming Hormone treatment via physiologic doses of oestrogen alone is insufficient to suppress testosterone levels into the normal range for natal females and addition of an anti-androgen is necessary. The use of an anti-androgen will continue to be available for this purpose in natal males, not before middle adolescence, who are prescribed Gender Affirming Hormones from around 16 years of age, and for natal males who are aged 17 years and above who are seen by adult Gender Dysphoria Clinics. NHS England has concluded that no direct or indirect discrimination arises because the use of GnRHa alongside Gender Affirming Hormones is not clinically indicated in natal females. <u>Comparator Group – Children with Central Precocious Puberty</u> Consideration must also be given as to whether direct or indirect discrimination arises in regard to individuals who share this protected characteristic, as GnRHa will continue to be routinely available through	

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	NHS protocols[14] for children who present with Central Precocious Puberty (CPP)[15]. This is a rare disease[16] caused by premature reactivation of the hypothalamic-pituitary-gonadal axis, resulting in the premature development of pubertal pulsatile secretion of gonadotropins in childhood. GnRHa is standard of care as a response to CPP (where patients meet clinical criteria) and the clinical approach is not contested. The various available agents have been licensed for CPP in the UK[17] and in many other countries for over 25 years following a consideration of the outcome of a number of clinical trials[18]. By contrast, GnRHa is not authorised for use in gender incongruence – they are in use 'off-label' – there is limited evidence on treatment aims, benefits, risks	

[14] NHS England is not the responsible commissioner of clinical interventions for children with a diagnosis of Central Precocious Puberty; this responsibility rests with Integrated Care Boards who form their own clinical commissioning policies in regard to their own populations.
[15] GnRHa is also licensed as a response to various cancers and endometriosis in adults – these patient groups are not regarded as appropriate comparators for the purpose of this EHIA.
[16] The true epidemiology of CPP is unknown. A US study estimated that CPP in the general population was between 1:5000 to 1:10,000 children; in Europe, a Danish national study reported the prevalence of CPP as 0.2% for girls and less than 0.05% for boys; Spanish and French studies showed different annual incidence of CPP in both sexes; Mucaria, 2021
[17] British National Formulary for Children, National Institute for Health and Care Excellence
[18] A drug will only be licensed for a specific indication if there is good quality evidence around treatment aims, risks, benefits and outcomes.

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	and outcomes;[19] and the clinical approach is contested[20]. In considering whether discrimination arises, it must be understood that the aetiology and epidemiology of CPP and treatment aims are quite different to that of gender incongruence. CPP is the *early onset* of puberty and secondary sexual characteristics (generally accepted as <8 years in girls and <9 years in boys) and it can range in seriousness from benign to malignant variants. The cause is often unclear but it can be attributable to a number of conditions that may require specialist investigation (Central Nervous System (CNS) tumours; CNS head trauma; genetics; neurofibromatosis type-1; cerebral palsy - *not exhaustive*). GnRHa for this cohort will be considered if the child has rapidly progressing symptoms or if bone age is significantly advanced beyond birth age. The physiological aims of GnRHa as a response to CPP are to halt pubertal progression and	

[19] Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria; National Institute for Health and Care Excellence, 2020

[20] Interim report of the Cass Review, 2022

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	progressive physical development and to preserve or reclaim adult height potential. NHS England has concluded that no direct discrimination occurs. NHS England has also concluded that no indirect discrimination arises by virtue of the fact that GnRHa will continue to be routinely commissioned for this appropriate comparator group. The evidence base that supports the administration of GnRHa as a response to CPP is strong and the clinical approach is not contested; the aetiology and epidemiology of CPP is quite different to that of gender incongruence, though the aetiology of gender incongruence is in itself still largely unidentified[21].	
Marriage & Civil Partnership: people married or in a civil partnership.	NHS England is in receipt of no evidence to suggest otherwise and therefore is of the view that the proposed interim service specification does not have any significant impact on individuals who may share this protected characteristic.	

[21] Claahsen - van der Grinten, H., Verhaak, C., Steensma, T. *et al.* Gender incongruence and gender dysphoria in childhood and adolescence—current insights in diagnostics, management, and follow-up. *Eur J Pediatr* **180**, 1349–1357 (2021).

<table>
<tr><th>Protected characteristic groups</th><th>Summary explanation of the main potential positive or adverse impact of your proposal</th><th>Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact</th></tr>
<tr><td>Pregnancy and Maternity: women before and after childbirth and who are breastfeeding.</td><td>NHS England is in receipt of no evidence to suggest otherwise and therefore is of the view that the proposed interim service specification does not have any significant impact on individuals who may share this protected characteristic.</td><td></td></tr>
<tr><td>Race and ethnicity[22]</td><td>Table: Children and young people referred to the current commissioned service between July and December 2022[23]
<table>
<tr><th colspan="3">GIDS: Q2 & Q3 Referred Patient Ethnicities</th></tr>
<tr><th>Ethnic Group</th><th>Count</th><th>%</th></tr>
<tr><td>Any Other Ethnicity</td><td>3</td><td>0.6%</td></tr>
<tr><td>Asian or Asian British – Any Other</td><td>5</td><td>1.0%</td></tr>
<tr><td>Asian or Asian British – Indian</td><td>1</td><td>0.2%</td></tr>
<tr><td>Black or Black British – Caribbean</td><td>2</td><td>0.4%</td></tr>
<tr><td>Mixed – Any Other Background</td><td>15</td><td>3.0%</td></tr>
<tr><td>Mixed – White & Asian</td><td>1</td><td>0.2%</td></tr>
<tr><td>Mixed – White & Black Caribbean</td><td>2</td><td>0.4%</td></tr>
<tr><td>Not Known – Not Requested</td><td>1</td><td>0.2%</td></tr>
<tr><td>Not Stated – Client Unable to Choose</td><td>152</td><td>30.5%</td></tr>
<tr><td>Other Ethnic Group – Chinese</td><td>1</td><td>0.2%</td></tr>
<tr><td>White – Any Other Background</td><td>11</td><td>2.2%</td></tr>
</table></td><td>There is evidence that gender diverse individuals from BAME heritage are more likely to face discrimination on the basis of their race and gender and often within their religious community as well.

The reasons for the low numbers of people from BAME communities in the Tavistock data is not well understood.

NHS England's interim service specification for a new configuration of providers describes the importance of routine and consistent data collection, analysis and reporting. We expect providers to report demographic data for the purpose of continuous service improvement initiatives, including to identify whether any</td></tr>
</table>

[22] Addressing racial inequalities is about identifying any ethnic group that experiences inequalities. Race and ethnicity includes people from any ethnic group incl. BME communities, non-English speakers, Gypsies, Roma and Travelers, migrants etc.. who experience inequalities so includes addressing the needs of BME communities but is not limited to addressing their needs, it is equally important to recognise the needs of White groups that experience inequalities. The Equality Act 2010 also prohibits discrimination on the basis of nationality and ethnic or national origins, issues related to national origin and nationality.
[23] Source: Data return by Tavistock and Portman NHS Foundation Trust, February 2023

<table>
<tr><th>Protected characteristic groups</th><th>Summary explanation of the main potential positive or adverse impact of your proposal</th><th>Main recommendation from your proposal to reduce any key identified adverse impact or to increase the identified positive impact</th></tr>
<tr><td></td><td>
<table>
<tr><td>White – British</td><td>200</td><td>40.2%</td></tr>
<tr><td>White – Mixed White</td><td>2</td><td>0.4%</td></tr>
<tr><td>White – Polish</td><td>2</td><td>0.4%</td></tr>
<tr><td>Blank</td><td>100</td><td>20.1%</td></tr>
<tr><td>TOTAL</td><td>498</td><td></td></tr>
</table>

Analysis of ethnicity data from the Tavistock and Portman NHS Foundation Trust remains challenging given the (historically) high number of individuals seen by the GIDS for whom ethnicity data was not recorded or not available (50.8% of patient records according to the above table). An analysis by NHS England of ethnicity data relating to individuals on the waiting list that is now held by NHS AGEM Commissioning Support Unit is not possible as this data was not routinely recorded by the Tavistock GIDS at the point of referral.

Of the data available, the highest proportion of individuals are “White” which accords with previous NHS analyses of individuals accessing gender incongruence services.

A 2022 publication[24] reported that the majority of young people seen at the</td><td>particular groups are experiencing barriers in access to service provision.

At a broader level, in 2021 NHS England established the National Healthcare Inequalities Improvement Programme (HiQiP), which works with national programmes and policy areas across NHS England, to address inequalities and ensure equitable access, excellent experience and optimal outcomes. The terms of reference for the NHS England National Programme Board for Gender Dysphoria Services (2023 – 2026, to be agreed June 2023) will include a focus on addressing and reducing health inequalities aligned with the HiQiP.

Criteria for enrolment in a clinical study

Alongside the first proposed study, further engagement is also planned by the National Research Oversight Board to identify the key evidence gaps for children and young people with later-onset gender dysphoria – recognising that there is even greater uncertainty in terms of the supporting clinical evidence base, less established clinical practice and less known about the natural history of gender dysphoria in this group. The clinical study team has yet to define these terms.</td></tr>
</table>

[24] Manjra II, Russell I, Maninger JK, Masic U. Service user engagement by ethnicity groups at a children’s gender identity service in the UK. *Clinical Child Psychology and Psychiatry*. 2022;27(4):1091-1105.

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	Tavistock GIDS self-identified with a white ethnic-background (93.35%) and 6.65% identified as being from ethnic minority heritage. It concluded that service engagement was comparable between the subgroups, while the ethnic minority sub-group was offered and attended more appointments in 2018–2019. Due to the low ethnic minority sub-group numbers, findings need to be interpreted with caution. We may surmise that the policy may disproportionately impact individuals who are 'White". NHS England concludes that the policy does not unfairly discriminate against individuals who share this protected characteristic. A related issue is that we know from previous data collections that, generally, there is under-representation of people from Black, Asian and Minority Ethnic hertiage accessing gender dysphoria services in England. The Office for National Statistics has advised (November 2023), following analysis of the 2021 UK census, that "*the trans population is not spread equally across all groups of the population [which] made up 0.3% in the White [ethnic groups] compared with 1.6% of people in the black, Black British, Black*	

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	Welsh, Caribbean or African ethnic group" though the report notes the possibility of that respondents whose first language is not English or Welsh may not have understood the question as intended.	
Religion and belief: people with different religions/faiths or beliefs, or none.	There is limited available evidence on the religious attitudes of trans people in the United Kingdom, although The Trans Mental Health Study found that most people who took part stated that they had no religious beliefs (62%). A data collection exercise of adult Gender Dysphoria Clinics undertaken by NHS England in 2016 reaffirmed the findings of this study but it is unclear as to the extent to which the findings may relate to children and young people. NHS England is of the view that the policy does not significantly impact individuals who share this protected characteristic.	
Sex: men; women	At current referral patterns 69% of referrals to the current commissioned service at Tavistock GIDS are of natal females and 31% are of natal males[25]. This data accords with figures published by the Cass Review in March 2022 that show a	The terms of reference for the Cass Review include *"exploration of the reasons for the increase in referrals and why the increase has disproportionately been of natal females, and the implications of these matters".*

[25] Source: Data return by Tavistock and Portman NHS Foundation Trust, February 2023

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	trend since 2011 in which the number of natal females is higher than the number of natal males being referred. Prior to that the split in the caseload was roughly even between natal girls and natal boys, but by 2019 the split had changed so that 76% per cent of referrals were natal females. That change in the proportion of natal girls to boys is reflected in the statistics from the Netherlands (Brik et al "*Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria"* 2018). The policy may disproportionately impact individuals who are natal female based on this data. NHS England has concluded that no direct or indirect discrimination arises. The policy is a reasonable, rational and clinically necessary response to the findings of NICE and the Cass Review that a key limitation to identifying the effectiveness and safety of GnRHa in regard to children and young people with gender incongruence is the lack of reliable comparative studies. The independent report on the analysis of responses to NHS England's separate public consultation on a proposed interim service specification for gender incongruence	NHS England's proposed interim service specification for a new configuration of providers describes the importance of building research capabilities for the purpose of continuous quality improvement initiatives. Also, in 2019 the Government Equalities Office announced that it would commission new research to explore the nature of adolescent gender identity and transitioning to better understand the issues behind the increasing trend of referrals of adolescents to NHS gender dysphoria service. Working with the new configuration of service providers and academic partners, NHSE will consider how to use the outcome of this research to inform its future approach to the commissioning of these services. *Criteria for enrolment in a clinical study* Alongside the first proposed study, further engagement is also planned by the National Research Oversight Board to identify the key evidence gaps for children and young people with later-onset gender dysphoria – recognising that there is even greater uncertainty in terms of the supporting clinical evidence base, less established clinical practice and less known about the natural history of gender dysphoria in this group. The clinical study team has yet to define these terms.