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Feminising medicines comprising oestrogen monotherapy for children and young people with gender incongruence who identify as a female gender and wish to undergo a binary physical transition

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NHS England Evidence Review

Feminising medicines comprising oestrogen monotherapy for children and young people with gender incongruence who identify as a female gender and wish to undergo a binary physical transition

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of feminising medicines comprising oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or no intervention, for children and young people (CYP) with gender incongruence who identify as female and wish binary physical transition.

The International Classification of Diseases (ICD)-11 (WHO, 2025) splits gender incongruence into that identified in childhood and that identified in adolescents and adults. Gender incongruence of childhood is characterised by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. The incongruence must have persisted for about two years. Gender incongruence of adolescence and adulthood is a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

Although the diagnosis of gender incongruence includes both adolescence and adulthood, this evidence review refers specifically to CYP up to their 18th birthday.

Treatment for gender incongruence aims to help people live the way they want to, in their preferred gender identity, whilst aiming to improve mental health and quality of life outcomes. Feminising medicines are used to help treat gender incongruence and make the patient's body more congruent with their gender identity. Treatment includes oestrogen which will result in the patient's body developing a more female physical appearance. These treatments will be used in combination with a number of other interventions. This evidence review focusses on individuals that use oestrogen monotherapy.

Studies in which GnRH analogues are used in the context of puberty suppression or used as puberty suppressing hormones are outside of the scope of this evidence review. NHS England and the National Institute of Health and Care Research (NIHR) are working together to set up a study into the potential benefits and harms of puberty suppressing hormones as a treatment option for CYP with gender incongruence.

In addition, the review scope included the identification of possible subgroups of CYP within the included studies who might benefit from treatment with oestrogen monotherapy more than the wider population, the criteria used by research studies to define gender incongruence, oestrogen dosing regimens, circumstances in which any CYP aged 15 years

or younger received oestrogen monotherapy, monitoring arrangements and study exclusion criteria.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of feminising medicines comprising oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to female or no intervention, for CYP with gender incongruence who identify as female and wish a binary physical transition.

The terminology in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'CYP who identify as a female gender and wish a binary physical transition' rather than saying natal or biological sex and 'cross-sex hormones' are now referred to as 'masculinising or feminising medicines.' The studies referenced in this review may use historical terms which are no longer considered appropriate (Table 1, Appendix E: Evidence Table, Appendix G: GRADE profiles).

The searches for evidence published since 01 January 2005 were conducted on 04 June 2025 and identified 1,233 references. These were screened using their titles and abstracts, and 69 full text papers were obtained and assessed for relevance against the criteria defined in the PICO for this review.

Four studies were identified for inclusion in this evidence review (Allen et al 2019, Grannis et al 2023, Kramer et al 2024 and Valentine et al 2022). Of the four included studies, three provided comparator evidence. All three studies providing comparator evidence were cross-sectional studies (Grannis et al 2023, Kramer et al 2024 and Valentine et al 2022). The final study, Allen et al (2019), was a retrospective cohort study but did not include an in-scope comparator group. The number of individuals in the studies ranged from 14 in Allen et al (2019) to 349 in Valentine et al (2022). Two studies reported mean and median duration of treatment (Allen et al 2019, median 349 days; Grannis et al 2023, mean 13.53 months).

Evidence was available for all the critical outcomes of interest: one cross-sectional study for impact on gender incongruence (Grannis et al 2023), two cross-sectional studies and one retrospective cohort study provided evidence for impact on mental health (Allen et al 2019, Grannis et al 2023 and Kramer et al 2024) and one retrospective cohort study provided non-comparator evidence for impact on quality of life (Allen et al 2019).

No evidence was available for any of the important outcomes of interest: feminising physical changes, psychosocial impact, fertility, feasibility of feminising genital surgery, cognitive outcomes, detransition after receipt of feminising medicines and regret after receipt of

feminising medicines. One cross-sectional study provided comparator evidence for safety (Valentine et al 2022).

No evidence was identified for cost-effectiveness or any subgroups of interest.

All of the evidence was from children and young people with gender incongruence attending gender incongruence clinics at private paediatric hospitals in the United States of America.

The included studies all provided very low certainty evidence for all the outcomes reported when assessed using modified GRADE.

In terms of clinical effectiveness:

Critical outcomes

Impact on gender incongruence

- *Oestrogen monotherapy vs no hormones*

  One cross-sectional study reported a lower mean body image dissatisfaction score in CYP who identify as a female gender wishing a binary physical transition receiving oestrogen monotherapy, when compared to those not receiving oestrogen, for a mean of 13.5 months; the results were *not statistically significant*. The same study reported *a statistically significant difference* in the body image dissatisfaction score between those on oestrogen monotherapy, compared to those not on oestrogen, but receiving other feminising medicines or no feminising medicines (effect size and direction not reported).

- *Oestrogen monotherapy (no comparator)*

  No evidence was identified for this outcome

Impact on mental health

- *Oestrogen monotherapy vs no hormones*

  One cross-sectional study reported *statistically significantly higher* depressive symptoms (mean score[1], oestrogen: 18.13 vs no oestrogen: 15.47) and levels of suicidality (mean score[2], oestrogen: 2.73 vs no oestrogen: 2.18) in CYP with gender incongruence and wishing a binary physical transition receiving oestrogen monotherapy when compared to those not receiving oestrogen, for a mean of 13.5 months.

[1] A higher score indicates a higher level of depressive symptoms
[2] Suicidality was measured by counting the frequency of suicidal ideation and/or attempts in the past year

The same study reported *statistically significantly higher* levels of social anxiety (mean score[3], oestrogen: 64.07 vs no oestrogen: 59.53) in CYP receiving oestrogen monotherapy when compared to those not receiving oestrogen, but overall anxiety scores were *not statistically significantly different*.

A second cross-sectional study reported both *statistically significantly higher* levels and *statistically significantly higher* odds of objective binge eating in CYP with gender incongruence receiving oestrogen monotherapy, for a binary physical transition, when compared to those not receiving oestrogen (OR 4.83, 95% CI 1.23 to 18.98). There were *no statistically significant differences* in the prevalence of other disordered eating symptoms (subjective binge eating, self-induced vomiting, laxative use and compensatory exercise) between CYP taking oestrogen monotherapy for gender incongruence and those not taking hormones.

- *Oestrogen monotherapy (no comparator)*

  One retrospective cohort study reported lower levels of suicidality in CYP following three months of oestrogen monotherapy for a binary physical transition when compared to baseline; the results were not compared statistically.

Impact on quality of life

- *Oestrogen monotherapy vs no hormones*

  No evidence was identified for this outcome.

- *Oestrogen monotherapy (no comparator)*

  One retrospective cohort study reported higher levels of well-being in CYP who identify as a female gender wishing a binary physical transition following three months of oestrogen monotherapy when compared to baseline; the results were not compared statistically.

Important outcomes

Feminising physical changes

- No evidence was identified for feminising physical changes.

Psychosocial impact

- No evidence was identified for psychosocial impact.

Fertility

[3] Higher values indicate greater social anxiety

- No evidence was identified for fertility.

Feasibility of feminising genital surgery

- No evidence was identified for feasibility of feminising genital surgery.

Cognitive outcomes

- No evidence was identified for cognitive outcomes.

Detransition after receipt of feminising medicines

- No evidence was identified for detransition after receipt of feminising medicines.

Regret after receipt of feminising medicines

- No evidence was identified for regret after receipt of feminising medicines.

In terms of safety:

- *Oestrogen monotherapy vs no hormones*

  One cross-sectional study reported *statistically significantly higher* odds of dyslipidaemia, hypertension and liver dysfunction when comparing CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy for an unknown duration to those not receiving hormones; the odds were *no longer statistically significant* following adjustment for confounders.

- *Oestrogen monotherapy (no comparator)*

  No evidence was identified for this outcome

In terms of cost effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- No evidence was identified for any subgroups of patients that may benefit more than the wider population of interest.

In terms of criteria used by the research studies to define gender incongruence:

- None of the included studies provided a definition of gender incongruence. Three of the studies referred to gender dysphoria when describing study participants. Two of the included studies simply noted that the included participants should have a *"diagnosis of gender dysphoria"*, whilst one cross-sectional study described participants being eligible for inclusion if they met "diagnostic classification of gender

dysphoria based on comprehensive mental health evaluation by a provider specialising in gender development."

In terms of the starting criteria, formulation, duration and dose of oestrogen treatment:

- No evidence was identified for oestrogen dosing.

In terms of CYP aged 15 years and younger that received oestrogen monotherapy:

- One retrospective cohort study and three cross-sectional studies provided information on the age range of individuals included in their studies. None of the authors gave any information about a minimum age requirement for oestrogen initiation.

In terms of the monitoring arrangements that were in place for CYP with gender incongruence who identify as female and wish a binary transition receiving feminising medicines, comprising of oestrogen monotherapy:

- No evidence was identified regarding monitoring arrangements for CYP receiving feminising medicines.

In terms of the exclusion criteria of the studies:

- No studies provided exclusion criteria. One retrospective cohort study and three cross-sectional studies provided inclusion criteria.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

Evidence was identified for all the critical outcomes of interest and for safety. No evidence was identified for any of the important outcomes of interest, subgroups or cost-effectiveness. The outcomes reported were primarily objective or assessed using standard assessment tools. The use of standardised outcome measures allows some interpretation of the level of burden associated with specific scores; however, it was not clear how clinically significant the changes observed were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

Most of the studies included populations, interventions or both which were not directly related to those specified for this evidence review. Three of the studies included both adolescents and adults, two included gender non-binary as well as binary individuals and in

three of the studies some of the intervention or the comparator group received other feminising medicines. Only two of the four studies reported the duration of treatment with oestrogen monotherapy and other treatments received were not reported. All four studies were based in private clinics in the USA; it is not clear if the individuals and aspects of care in the study reflect those seen in clinical practice in England and care is needed in generalising results to the NHS.

All of the included studies were judged to be at high risk of bias and the outcomes reported were assessed as very low certainty evidence when evaluated using modified GRADE. Of particular note was the lack of reporting of psychological or psychosocial support / interventions in both the intervention and control populations; this increases the risk of bias through potential confounding. Limitations reducing the certainty of the outcomes included limited information about patient baseline demography and clinical characteristics (Valentine et al 2022) and differences in baseline demography between groups (Grannis et al 2023); both of these increase selection bias. Three of the studies lacked identification or adjustment for potential confounding factors (Allen et al 2019, Grannis et al 2023 and Kramer et al 2024). Two studies were missing crucial information about the control population (Valentine et al 2022) or intervention (Kramer et al 2024). Furthermore, three of the included studies (Grannis et al 2023, Kramer et al 2024 and Valentine et al 2022), all of the studies with comparator evidence, were cross-sectional studies which limit the assessment of causality; since both the outcomes and the exposure (in this case oestrogen monotherapy) are measured at the same point in time, it is impossible to determine temporality, and these types of studies can only demonstrate associations.

Conclusion

This review included four studies comparing the clinical effectiveness of feminising medicines, comprising oestrogen monotherapy, to one or a combination of psychological support or social transitioning to the desired gender, or no intervention, for children and young people (CYP) with gender incongruence who identify as a female gender and wish a binary physical transition.

Data were available for all the critical outcomes of interest and for safety. All evidence was of very low certainty when assessed using modified GRADE. No evidence was available for any of the important outcomes of interest. The comparator studies compared oestrogen monotherapy with no oestrogen; no studies were found comparing oestrogen to psychological support or social transitioning. No evidence was identified for cost-effectiveness or subgroups.

Much of the evidence was indirect due to the inclusion of mixed populations or interventions which are out-of-scope for this evidence review. For example, some populations included adults or non-binary individuals and some of those in the intervention or comparator group received other feminising medicines.

One analytical cross-sectional study provided evidence for impact on gender incongruence, reporting a statistically significant difference in the body image dissatisfaction score (but no indication of effect size or direction) between those on oestrogen monotherapy compared to those on other feminising medicines and those not on any feminising medicines. The evidence around the impact of feminising medicines on mental health was mixed with one cross-sectional study reporting statistically significantly higher levels of depression, social anxiety and suicidality, but no statistically significant difference in levels of anxiety, in those treated with oestrogen monotherapy compared with those not receiving oestrogen. One cross-sectional study reported statistically significantly higher levels of objective binge eating, but no statistically significant difference in other disordered eating symptoms in those treated with oestrogen monotherapy compared with those not receiving oestrogen. A retrospective cohort study found a lower level of suicidality following treatment with oestrogen monotherapy, and for impact on quality of life, the same study found that reported well-being was improved, but no statistical tests were reported.

Safety was reported in one cross-sectional study. The study reported statistically significant increased odds of dyslipidaemia, hypertension and liver dysfunction in CYP with gender incongruence on oestrogen monotherapy, compared to individuals not on oestrogen, in unadjusted analyses. These results were no longer statistically significant after adjusting for confounding factors.

Overall, there is very low certainty evidence with inconsistent results for the selected outcomes in CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy. There is also a lack of direct evidence due to the mixed populations and mixed interventions which further limits the conclusions that can be drawn. No conclusions can be drawn about cost-effectiveness as no evidence was identified. Published studies which allow conclusions to be drawn about the effectiveness of oestrogen monotherapy for this population are needed.

3. Methodology

Review questions

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

1. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the clinical effectiveness of treatment with oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
2. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the short-term and long-term safety of oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
3. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the cost-effectiveness of oestrogen monotherapy with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition that may benefit more from treatment with oestrogen monotherapy than the wider population?
5. From the evidence selected:
    a) What were the criteria used by the research studies to define gender incongruence?
    b) What were the starting criteria, formulation, duration and dose of oestrogen monotherapy for those aged 16 years up to their 18th birthday?
    c) Did any children aged 15 years or younger receive oestrogen monotherapy for gender transition? If so, in what circumstances?
    d) What monitoring was in place for CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition receiving oestrogen monotherapy?
    e) What were the exclusion criteria in the studies?

See Appendix A for the full PICO document.

Review process

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

The searches for evidence were informed by the PICO document and were conducted on 04 June 2025.

See Appendix B for details of the search strategy.

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

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

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

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

Four studies were identified for inclusion in this evidence review (Allen et al 2019, Grannis et al 2023, Kramer et al 2024 and Valentine et al 2022). Of the four included studies, three were cross-sectional studies providing comparator evidence (Grannis et al 2023, Kramer et al 2024 and Valentine et al 2022). The final study, Allen et al (2019), was a retrospective cohort study but its comparator group was not in-scope for this review.

Evidence was available for all the critical outcomes of interest: one cross-sectional study for impact on gender incongruence, two cross-sectional studies and one retrospective cohort study provided evidence for impact on mental health and one retrospective cohort study provided non-comparator evidence for impact on quality of life.

No evidence was available for any of the important outcomes of interest: feminising physical changes, psychosocial impact, fertility, feasibility of feminising genital surgery, cognitive outcomes, detransition after receipt of feminising medicines and regret after receipt of feminising medicines. One cross-sectional study provided comparator evidence for safety.

No evidence was identified for cost-effectiveness or any subgroups of interest.

The terminology in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase ‘children and young people with gender incongruence who identify as a female gender and wish to undergo a binary physical transition’ rather than saying natal or biological sex and ‘cross-sex hormones’ are now referred to as ‘masculinising or feminising medicines.’ The data extracted from studies into Table 1, Appendix E: Evidence Table and Appendix G: GRADE profiles may use historical terms which are no longer considered appropriate.

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

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Allen et al 2019 Retrospective cohort study USA (single centre)	14 AMAB GAH only: n=12[a] GAH+GnRH analogue: n=2 Age (years) at administration of GAH, mean (range): 16.59 (13.73 to 19.04)[b] No subgroups reported	**Intervention** GAH-only[a] Specific formulations and doses were not detailed **Comparators** None The use of other gender-affirming treatments such as surgery or psychological and	Median (SD) duration of treatment, for the whole cohort, was 349 days (193 days). Median duration for those AMAB was not reported. **Critical outcomes** **Impact on mental health** • Suicidality[c] **Impact on quality of life**

Study	Population	Intervention and comparison	Outcomes reported
		psychosocial interventions were not reported.	• Well-being[d]
Grannis et al 2023 Cross-sectional study USA (single centre)	32 AMAB Oestrogen only: n=15 No oestrogen[e]: n=17 Age (years), mean (SD): • Oestrogen: 17.64 (0.86) • No oestrogen: 16.27 (1.49) • p<0.01 No subgroups reported	**Intervention** Oestrogen monotherapy, in the form of transdermal patch or oral tablets[f] **Comparators** No oestrogen[e] The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	Mean (SD) duration of treatment was 13.53 months (8.69 months). **Critical outcomes** **Impact on gender incongruence** • Body image dissatisfaction[g] **Impact on mental health** • SCARED[h] • CDI[i] • LSAS[j] • Suicidality[k]

Kramer et al 2024
 	
Cross-sectional study
 	
USA (single centre)
	70 AMAB
	
	GAH: n=14
	
	No GAH: n=unclear[l]
	
	Age (years), mean (SD): 17.79 (3.12)
	
	No subgroups reported
		Intervention
		
		Gender-affirming hormones (GAH)[m]
		
		Comparators
		
		No GAH
		
		The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.
			Duration of treatment not reported
			
			Critical outcomes
			
			Impact on mental health
			
			• EDE-Q[n] ED Behaviours
			  ○ Subjective binge episode
			  ○ Objective binge episode
			  ○ Self-induced vomiting
			  ○ Laxative use
			  ○ Compensatory exercise

Valentine et al 2022 Cross-sectional study USA (six centres)	4,172 transgender and gender-diverse youth (TGDY)[o] 1,407 (33.7%) AMAB n=349 individuals on oestrogen monotherapy number of individuals not on gender affirming hormone treatment (GAHT) unclear[p] Age (years) at first visit, median (IQR): 10.0 (4.4 to 14.6)[q] Age (years) at last visit, median (IQR): 16.7 (14.6 to 18.3)[q] No subgroups reported	**Intervention** Prescription of oestrogen in electronic health record[r] (EHR) Specific formulations and doses were not detailed **Comparators** Not prescribed GAHT The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	Duration of treatment not reported **Safety[s]** • Dyslipidaemia • Hypertension • Liver dysfunction

Abbreviations

AMAB: assigned male at birth; ASQ: Ask Suicide-Screening Questions; CDI: Children's Depression Inventory; ED: eating disorder; EDE-Q: Eating Disorder Examination-Questionnaire; EHR: electronic health record; GAH: gender affirming hormones; GAHT: gender affirming hormone therapy / gender affirming hormone treatment; GnRH:

Study	Population	Intervention and comparison	Outcomes reported
gonadotropin-releasing hormone; GWBS: PedsQL General Well-Being Scale; IQR: interquartile range; LSAS: Leibowitz Social Anxiety Score; n: number; PCOS: polycystic ovary syndrome; SAD: Social Anxiety Disorder; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; TGD: transgender and gender diverse; TGDY: transgender and gender diverse youth; USA: United States (of America)			

Footnotes

a. GAH-only was specified as participants that did not receive GnRH analogues prior to being administered GAH. No further details of exact medications supplied. The authors reported that the endocrinologists in their clinic sometimes begin participants at hormone levels lower than the recommended protocol, and typically, patients' doses are gradually increased every three to six months so that the dosage levels recommended by suggested protocols are reached by the end of treatment. n=14 AMAB participants: n=12 received GAH-only, n=2 received GAH+GnRH analogues. Results for CYP AMAB that received GAH-only were not presented separately

b. This number differed from Table 1 and the text. The number here is that reported in the text

c. Suicidality was measured using the Ask Suicide-Screening Questions (ASQ). The ASQ is a four-item measure used to identify patients who are at risk of attempting suicide. Questions include: In the past few weeks have you… "…wished you were dead?", "…felt that you or your family would be better off if you were dead?", "…been having thoughts about harming or killing yourself?", or "…done anything to hurt yourself or to end your life?" The final question was modified from a lifetime risk of suicidality to risk of suicidality in the previous few weeks. Prior to 2017, the final question was not asked, and the score was imputed using expectation maximisation. A response of "no" was scored as 0 and a response of "yes" was scored as 1; with an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation

d. Well-being was measured using the PedsQL General Well-Being Scale (GWBS). The GWBS is a 5-point response scale, containing seven items, and measures "general well-being" and "general health". The general well-being subscale includes six items (eg "I feel happy" and "I think my health will be good in the future"). Participants are asked to consider each item over the past month and rate responses from 0 (never) to 4 (almost always). The general health subscale contains one item, "In general, how is your health?" ranging from 0 (Bad) to 4 (Excellent). All items are scored and linearly transformed to a 0 to 100 scale (initial score of 0 = 0, 1 = 25, 2 = 50, 3 = 75, and 4 = 100). Higher scores indicate perceptions of minimal problems, high wellbeing

e. n=10 participants in the no oestrogen group were receiving either GnRH analogues (in the form of puberty blockers) or spironolactone rather than no GAHT at the time of data collection

f. Medication information came from electronic medical records

g. Body image dissatisfaction was measured to assess dysphoria related to various aspects of one's body; a specific screening tool was not detailed. Higher values indicate greater dissatisfaction with one's body image

h. The Screen for Child Anxiety Related Emotional Disorders (SCARED) is a self-completed questionnaire (with child/parent versions for those aged under 11 years), consisting of 41 items. Each question is graded on a scale of 0 – "Not True or Hardly Ever True"; 1 – "Somewhat True or Sometimes True"; or 2 – "Very True or Often True". A total score of ≥ 25 may indicate the presence of an Anxiety Disorder. Scores higher than 30 are more specific

i. The Children's Depression Inventory (CDI) is a self-report questionnaire developed by Maria Kovacs to assess cognitive, affective, and behavioural signs of depression in children and adolescents, typically aged seven to 17. It consists of 27 items that are scored on a 0-2 scale, based on the statements "…once in a while," "…many times," and "…all the time,", to indicate the severity of symptoms over the past two weeks, focusing on areas like negative mood, self-esteem, and interpersonal problems. A higher total score on the CDI indicates a higher level of depressive symptoms

j. The Liebowitz Social Anxiety Scale (LSAS) is a psychological assessment tool specifically designed to evaluate the range and severity of social anxiety disorder (SAD) symptoms. Respondents are asked to rate their level of fear or anxiety and the degree to which they avoid specific social and performance situations on a scale from 0 to 3, higher values indicate greater social anxiety

k. Suicidality was measured by counting the frequency of suicidal ideation and/or attempts in the past year

l. The authors note that data regarding use of gender-affirming hormone use was not available for n=63 of the total sample of TGD (including both AMAB and AFAB). It is not stated how many of those with unknown data are AMAB. Outcomes for AMAB with no GAH are reported for n of between 35 and 39.

m. The authors do not specify the GAH used but state "28% of TGD youth (n=53) reported prior use of gender-affirming hormones, including [o]estrogen (n=15) and testosterone (n=39)"

n. The Eating Disorder Examination-Questionnaire (EDE-Q) is a self-report questionnaire measuring disordered eating attitudes and behaviours over the past 28-days and is widely used. The Global EDE-Q score is an average

Study	Population	Intervention and comparison	Outcomes reported
of the four subscales (Restraint, Weight Concern, Shape Concern and Eating Concern) with individual EDE-Q items reflecting specific disordered eating behaviours (e.g. objective and subjective binge eating, laxative use, etc). Higher scores indicate more disordered eating; a score above 4 is indicative of a potential clinical ED o. Transgender and gender diverse youth were defined as *"having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet concept ID…which includes codes extracted from the EHR problem list or diagnosis code from any encounter"* PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (cities not stated), Nationwide Children's Hospital (Columbus, Ohio), St. Louis Children's Hospital, and Seattle Children's Hospital p. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen only includes individuals who are AMAB only, but this is not explicitly stated in the paper q. Baseline characteristics were only presented for the full TGDY cohort and not reported separately for the AMAB population r. ATC and RxNorm codes were used to pull prescription information from the PEDSnet database: GnRH analogue (L02AE) and oestrogen (G03C, not including combined oral contraceptive, G03A) s. Outcomes were captured using SNOMED concept codes and were defined as having either a diagnosis (billing code, problem list) or at least two abnormal measurements (anthropometric or laboratory value) recorded in the electronic health records			

5. Results

For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the clinical effectiveness, short-term and long-term safety of treatment with oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender incongruence **Certainty of evidence:** Very low	*This outcome is important to patients because gender incongruence is associated with significant distress and problems functioning.* One cross-sectional study provided comparator evidence relating to impact on gender incongruence in CYP with gender incongruence who identify as a female gender and wish a binary physical transition taking oestrogen monotherapy. Mean duration of treatment was 13.53 months. *Oestrogen monotherapy vs no hormones* **At mean treatment duration of 13.53 months** • One cross-sectional study (Grannis et al 2022) reported that CYP with gender incongruence who identify as a female gender wishing a binary physical transition receiving oestrogen monotherapy (n=15) reported a lower mean body image dissatisfaction[4] score than those not receiving oestrogen (n=17[5]):oestrogen: mean 85.33 (SD 16.31) vs no oestrogen: mean 88.53 (SD 29.01); the results were *not statistically significant* (p value reported to be non-significant). **(VERY LOW)** • One cross-sectional study (Grannis et al 2022) reported that CYP with gender incongruence who identify as a female gender wishing a binary physical transition receiving oestrogen monotherapy (n=15), reported a *statistically significantly different* mean body image dissatisfaction score than those not receiving oestrogen (n=10 receiving puberty blockers or spironolactone and n=7 receiving no feminising medicines) (effect size and direction not reported, p=0.04). **(VERY LOW)** *Oestrogen monotherapy (no comparator)* No evidence was identified for this outcome. ***Oestrogen monotherapy vs no hormones*** **One cross-sectional study reported a lower mean body image dissatisfaction score in CYP who identify as a female gender wishing a binary physical transition receiving oestrogen monotherapy, when compared to those not receiving oestrogen, for a mean of 13.5 months;**

[4] Body image dissatisfaction was measured to assess dysphoria related to various aspects of one's body; a specific screening tool was not detailed. Higher values indicate greater dissatisfaction with one's body image
[5] n=10 AMAB in the no oestrogen group were receiving either GnRH analogues (in the form of puberty blockers) or spironolactone monotherapy rather than no hormones at the time of data collection

Outcome	Evidence statement
	the results were *not statistically significant*. The same study reported *a statistically significant difference* in the body image dissatisfaction score between those on oestrogen monotherapy, compared to those not on oestrogen, but receiving other feminising medicines or no feminising medicines (effect size and direction not reported). This study provided very low certainty evidence. ***Oestrogen monotherapy (no comparator)*** **No evidence was identified for this outcome**
Impact on mental health **Certainty of evidence:** Very low	*This outcome is important to patients because gender incongruence is associated with psychological distress which can lead to the development of mental health problems.* Two cross-sectional studies provided comparator evidence, and one retrospective cohort study provided non-comparator evidence relating to impact on mental health in CYP with gender incongruence who identify as a female gender and wish a binary physical transition taking oestrogen monotherapy. Mean duration of treatment ranged from 349 days/11.6 months to 13.53 months. *Oestrogen monotherapy vs no hormones* Depression **At mean treatment duration of 13.53 months** • One cross-sectional study (Grannis et al 2022) reported that CYP with gender incongruence wishing a binary physical transition and receiving oestrogen monotherapy (n=15) reported *statistically significantly higher* levels of depressive symptoms, measured with the Children's Depression Inventory[6], when compared to those not receiving oestrogen (n=17[7]) for a mean of 13.5 months (mean (SD); oestrogen: 18.13 (8.13) vs no oestrogen: 15.47 (7.14), p<0.05). **(VERY LOW)** Suicidality **At mean treatment duration of 13.53 months** • One cross-sectional study (Grannis et al 2022) reported that CYP with gender incongruence wishing a binary physical transition and receiving oestrogen monotherapy (n=15) reported *statistically significantly higher* levels of suicidality[8], when compared to those not receiving oestrogen (n=17) for a mean of 13.5 months (mean (SD); oestrogen: 2.73 (1.83) vs no oestrogen: 2.18 (1.38), p<0.05). **(VERY LOW)** Anxiety **At mean treatment duration of 13.53 months** • One cross-sectional study (Grannis et al 2022) reported that CYP with gender incongruence wishing a binary physical transition receiving

[6] The Children's Depression Inventory (CDI) is a self-report questionnaire developed by Maria Kovacs to assess cognitive, affective, and behavioural signs of depression in children and adolescents, typically aged seven to 17. It consists of 27 items that are scored on a 0-2 scale, based on the statements *"…once in a while," "…many times,"* and *"…all the time,"*, to indicate the severity of symptoms over the past two weeks, focusing on areas like negative mood, self-esteem, and interpersonal problems. A higher total score on the CDI indicates a higher level of depressive symptoms

[7] n=10 AMAB in the no oestrogen group were receiving either GnRH analogues (in the form of puberty blockers) or spironolactone monotherapy rather than no hormones at the time of data collection

[8] Suicidality was measured by counting the frequency of suicidal ideation and/or attempts in the past year

Outcome	Evidence statement
	oestrogen monotherapy (n=15) reported lower levels of anxiety, measured with the SCARED questionnaire[9], when compared to those not receiving oestrogen (n=17) for a mean of 13.5 months (mean (SD); oestrogen: 40.07 (20.17) vs no oestrogen: 41.29 (15.19)); the results were *not statistically significant* (p value reported to be non-significant). **(VERY LOW)** • One cross-sectional study (Grannis et al 2022) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen monotherapy (n=15) reported *statistically significantly higher* levels of social anxiety, measured with LSAS[10], when compared to those not receiving oestrogen (n=17) for a mean of 13.5 months (mean (SD); oestrogen: 64.07 (38.62) vs no oestrogen: 59.53 (32.94), p<0.05). **(VERY LOW)** <u>Disordered eating</u> **At unknown treatment duration / follow-up** • One cross-sectional study (Kramer et al 2024) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen monotherapy (n=14) reported lower levels of subjective binge eating, measured using the EDE-Q[11], when compared to those not receiving oestrogen (n=36) (oestrogen: 28.6% vs no oestrogen: 22.2%); the results were *not statistically significant* (p>0.05). **(VERY LOW)** • One cross-sectional study (Kramer et al 2024) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen monotherapy (n=14) reported *statistically significantly higher* levels of objective binge eating, measured using the EDE-Q, when compared to those not receiving oestrogen (n=35) for a binary physical transition (oestrogen: 50.0% vs no oestrogen: 17.1%; p=0.03). **(VERY LOW)** • One cross-sectional study (Kramer et al 2024) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen monotherapy (n=14), reported *statistically significantly higher* odds of objective binge eating, measured using the EDE-Q, when compared to those not receiving oestrogen (n=35) (OR=4.83, 95% CI 1.23 to 18.98). **(VERY LOW)** • One cross-sectional study (Kramer et al 2024) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen monotherapy (n=14) reported higher levels of self-induced vomiting, measured using the EDE-Q, when compared to those not

[9] The Screen for Child Anxiety Related Emotional Disorders (SCARED) is a self-completed questionnaire (with child/parent versions for those aged under 11 years), consisting of 41 items. Each question is graded on a scale of 0 – *"Not True or Hardly Ever True";* 1 – *"Somewhat True or Sometimes True"*; or 2 – *"Very True or Often True"*. A total score of ≥ 25 may indicate the presence of an anxiety disorder. Scores higher than 30 are more specific

[10] The Liebowitz Social Anxiety Scale (LSAS) is a psychological assessment tool specifically designed to evaluate the range and severity of social anxiety disorder (SAD) symptoms. Respondents are asked to rate their level of fear or anxiety and the degree to which they avoid specific social and performance situations on a scale from 0 to 3, higher values indicate greater social anxiety

[11] The Eating Disorder Examination-Questionnaire (EDE-Q) is a self-report questionnaire measuring disordered eating attitudes and behaviours over the past 28-days and is widely used. The Global EDE-Q score is an average of the four subscales (Restraint, Weight Concern, Shape Concern and Eating Concern) with individual EDE-Q items reflecting specific disordered eating behaviours (e.g. objective and subjective binge eating, laxative use, etc). Higher scores indicate more disordered eating; a score above 4 is indicative of a potential clinical ED

Outcome	Evidence statement
	receiving feminising medicines (n=35) (oestrogen: 14.3% vs no oestrogen: 8.5%); the results were *not statistically significant* (p>0.05). **(VERY LOW)** • One cross-sectional study (Kramer et al 2024) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen (n=14) reported higher levels of laxative use, measured using the EDE-Q, when compared to those not receiving oestrogen (n=39) (oestrogen: 21.4% vs no oestrogen: 12.8%); the results were *not statistically significant* (p>0.05). **(VERY LOW)** • One cross-sectional study (Kramer et al 2024) reported that CYP with gender incongruence wishing a binary physical transition receiving oestrogen monotherapy (n=14) reported higher levels of compensatory exercise, measured using the EDE-Q, when compared to those not receiving oestrogen (n=35) (oestrogen: 29.6% vs no oestrogen: 11.4%); the results were *not statistically significant* (p>0.05). **(VERY LOW)** *Oestrogen monotherapy (no comparator)* Suicidality **At mean treatment duration of 349 days / 11.6 months** • One retrospective cohort study (Allen et al 2019) reported that CYP with gender incongruence identifying as a female gender and wishing a binary physical transition had lower levels of suicidality, measured with the ASQ[12], following three months of oestrogen monotherapy (n=14[13]) when compared to baseline after a mean treatment duration of 11.6 months (mean (SE); baseline: 1.21 (0.36); 3 months after 1st dose of oestrogen: 0.24 (0.19)); results were not compared statistically. **(VERY LOW)** ***Oestrogen monotherapy vs no hormones*** **One cross-sectional study reported *statistically significantly higher* depressive symptoms (mean score, oestrogen: 18.13 vs no oestrogen: 15.47) and levels of suicidality (mean score, oestrogen: 2.73 vs no oestrogen: 2.18) in CYP with gender incongruence and wishing a binary physical transition receiving oestrogen monotherapy when compared to those not receiving oestrogen, for a mean of 13.5 months.** **The same study reported *statistically significantly higher* levels of social anxiety (mean score, oestrogen: 64.07 vs no oestrogen: 59.53) in CYP receiving oestrogen monotherapy when compared to those not receiving oestrogen, but overall anxiety scores were *not statistically significantly different*.**

[12] Suicidality was measured using the Ask Suicide-Screening Questions (ASQ). The ASQ is a four-item measure used to identify patients who are at risk of attempting suicide. Questions include: In the past few weeks have you… "…wished you were dead?", "…felt that you or your family would be better off if you were dead?", "…been having thoughts about harming or killing yourself?", or "…done anything to hurt yourself or to end your life?" The final question was modified from a lifetime risk of suicidality to risk of suicidality in the previous few weeks. Prior to 2017, the final question was not asked, and the score was imputed using expectation maximisation. A response of "no" was scored as 0 and a response of "yes" was scored as 1; with an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation

[13] n=14 AMAB participants: n=12 received GAH-only, n=2 received GAH+GnRH analogues. Results for CYP AMAB that received GAH-only were not presented separately

Outcome	Evidence statement
	A second cross-sectional study reported both *statistically significantly higher* levels and *statistically significantly higher* odds of objective binge eating in CYP with gender incongruence receiving oestrogen monotherapy, for a binary physical transition, when compared to those not receiving oestrogen (OR 4.83, 95% CI 1.23 to 18.98). There were *no statistically significant differences* in the prevalence of other disordered eating symptoms (subjective binge eating, self-induced vomiting, laxative use and compensatory exercise) between CYP taking oestrogen monotherapy for gender incongruence and those not taking hormones. ***Oestrogen monotherapy (no comparator)*** **One retrospective cohort study reported lower levels of suicidality in CYP following three months of oestrogen monotherapy for a binary physical transition when compared to baseline; the results were not compared statistically.** **All of the above studies provided very low certainty evidence.**
Impact on quality of life **Certainty of evidence:** Very low	*This outcome is important to patients because gender incongruence may be associated with a significant reduction in health-related quality of life.* One retrospective cohort study provided non-comparator evidence relating to impact on quality of life in CYP with gender incongruence who identify as a female gender and wish a binary physical transition taking oestrogen monotherapy. Mean duration of follow-up was 349 days / 11.6 months. *Oestrogen monotherapy vs no hormones* No evidence was identified for this outcome. *Oestrogen monotherapy (no comparator)* **At mean treatment duration of 349 days / 11.6 months** • One retrospective cohort study (Allen et al 2019) reported that CYP with gender incongruence identifying as a female gender and wishing a binary physical transition had higher levels of well-being, measured with the PedsQL General Well-Being Scale[14], following three months of oestrogen monotherapy (n=14[15]), when compared to baseline; baseline: mean 58.44 (SE 4.09); 3 months after 1st dose of feminising medicines: mean 69.52 (SE 3.62)); results were not compared statistically. **(VERY LOW)** ***Oestrogen monotherapy vs no hormones*** **No evidence was identified for this outcome.** ***Oestrogen monotherapy (no comparator)***

[14] Well-being was measured using the PedsQL General Well-Being Scale (GWBS). The GWBS is a 5-point response scale, containing seven items, and measures "general well-being" and "general health". The general well-being subscale includes six items (eg "I feel happy" and "I think my health will be good in the future"). Participants are asked to consider each item over the past month and rate responses from 0 (never) to 4 (almost always). The general health subscale contains one item, "In general, how is your health?" ranging from 0 (Bad) to 4 (Excellent). All items are scored and linearly transformed to a 0 to 100 scale (initial score of 0 = 0, 1 = 25, 2 = 50, 3 = 75, and 4 = 100). Higher scores indicate perceptions of minimal problems, high wellbeing

[15] n=14 AMAB participants: n=12 received GAH-only, n=2 received GAH+GnRH analogues. Results for CYP AMAB that received GAH-only were not presented separately

Outcome	Evidence statement
	One retrospective cohort study reported higher levels of well-being in CYP who identify as a female gender wishing a binary physical transition following three months of oestrogen monotherapy when compared to baseline; the results were not compared statistically. This study provided very low certainty evidence.
Important outcomes	
Feminising physical changes **Certainty of evidence:** Not applicable	*This outcome is important because most patients with gender incongruence wish to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender.* **No evidence was identified for this outcome**
Psychosocial impact **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning.* **No evidence was identified for this outcome.**
Fertility **Certainty of evidence:** Not applicable	*This outcome is important to patients because feminising medicines can reduce fertility. Prior to commencing feminising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* **No evidence was identified for this outcome.**
Feasibility of feminising genital surgery **Certainty of evidence:** Not applicable	*This outcome is important to patients because feminising medicines can have an impact on surgical outcomes. Treatments may alter the amount of genital tissue available for vaginoplasty, clitoroplasty and/or vulvoplasty.* **No evidence was identified for this outcome.**
Cognitive outcomes **Certainty of evidence:** Not applicable	*This outcome is important to patients because feminising medicines can negatively impact cognitive processes such as concentration, memory, and executive function.* **No evidence was identified for this outcome.**
Detransition after receipt of feminising medicines **Certainty of evidence:** Not applicable	*Medical detransition is a complex experience encompassing medical, psychological, social implications and is important to patients because they may choose to discontinue treatment. The decision to detransition may or may not be associated with regret.* **No evidence was identified for this outcome.**
Regret after receipt of feminising medicines **Certainty of evidence:** Not applicable	*This outcome is important to patients because some patients who choose to take feminising medicines may regret this decision. Regret may or may not be associated with detransition.* **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** Very low	*It is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long-term effects that may impact on decisions for transitioning.*

Outcome	Evidence statement
	One cross-sectional study provided comparator evidence relating to safety in CYP with gender incongruence who identify as a female gender and wish a binary physical transition taking oestrogen monotherapy. Mean duration of treatment and follow-up was unknown. *Oestrogen monotherapy vs no hormones* **At unknown treatment duration** • One cross-sectional study (Valentine et al 2022) reported that CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy (n=349) had a *statistically significantly increased* odds of dyslipidaemia compared to individuals not on hormones (n is unclear[16]) (OR 1.9 (95% CI 1.3 to 2.7), p=0.001); this was *not statistically significant* after adjusting for confounders[17] (results not presented). **(VERY LOW)** • One cross-sectional study (Valentine et al 2022) reported that CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy (n=349) had a *statistically significantly increased* odds of hypertension compared to individuals not on hormones (n is unclear) (OR 2.3 (95% CI 1.7 to 3.2), p<0.0001); this was *not statistically significant* after adjusting for confounders (results not presented). **(VERY LOW)** • One cross-sectional study (Valentine et al 2022) reported that CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy (n=349) had a *statistically significantly increased* odds of liver dysfunction compared to individuals not on hormones (n is unclear) (OR 1.6 (95% CI 1.2 to 2.3), p=<0.01); this was *not statistically significant* after adjusting for confounders (results not presented). **(VERY LOW)** ***Oestrogen monotherapy vs no hormones*** **One cross-sectional study reported *statistically significantly higher* odds of dyslipidaemia, hypertension and liver dysfunction when comparing CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy for an unknown duration to those not receiving hormones; the odds were *no longer statistically significant* following adjustment for confounders.** **This study provided very low certainty evidence.** ***Oestrogen monotherapy (no comparator)*** **No evidence was identified for this outcome**
Abbreviations AMAB: assigned male at birth; ASQ: Ask Suicide-Screening Questions; CDI: Children's Depression Inventory; CI: confidence interval; CYP: children and young people; ED: eating disorder; EDE-Q: Eating Disorder Examination-Questionnaire; EHR: electronic health record; GAH: gender affirming hormones; GAHT: gender affirming hormone therapy / gender affirming hormone treatment; GD: gender dysphoria;	

[16] We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen and GnRH analogues includes individuals who are AMAB only, but this is not explicitly stated in the paper
[17] Analyses were adjusted for electronic health record recorded sex / sex assigned at birth, age at last visit, duration in PEDSnet / EHR, overweight / obesity status, depression status and antipsychotic prescription

Outcome	Evidence statement
GnRH: gonadotropin-releasing hormone; GWBS: PedsQL General Well-Being Scale; LSAS: Leibowitz Social Anxiety Score; n: number; OR: odds ratio; PCOS: polycystic ovary syndrome; SAD: Social Anxiety Disorder; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; SE: standard error; vs: versus	

In CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the cost-effectiveness of treatment with oestrogen monotherapy with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for cost-effectiveness.**

From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition that may benefit more from treatment with oestrogen monotherapy than the wider population?

Subgroup	Evidence statement
	No evidence was identified for subgroups.

From the evidence selected:

a) **What were the criteria used by the research studies to define gender incongruence?**
b) **What were the starting criteria, formulation, duration and dose of oestrogen for those aged 16 up to their 18th birthday?**
c) **Did any CYP aged 15 years or younger receive oestrogen monotherapy for gender transition? If so, in what circumstances?**
e) **What monitoring was in place for CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition receiving oestrogen monotherapy?**
f) **What were the exclusion criteria in the studies?**

Outcome	Evidence statement
Definitions of gender incongruence	None of the included studies provided a definition of gender incongruence. Two cross-sectional studies and one retrospective cohort study referred to gender dysphoria when describing study participants. • One retrospective cohort study (Allen et al 2019) did not define gender incongruence but reported that to access gender-affirming hormones, a

Outcome	Evidence statement
	"diagnosis of GD and a referral for medical treatment by a medical professional is required." • One cross-sectional study (Grannis et al 2023) noted that participants were eligible for inclusion if they met *"diagnostic classification of gender dysphoria based on comprehensive mental health evaluation by a provider specialising in gender development."* • One cross-sectional study (Valentine et al 2022) defined transgender and gender diverse youth as *"having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet[18] concept ID)."* No further details *of "related diagnoses"* were provided.
Oestrogen dosing	No evidence was identified for oestrogen dosing.
Oestrogen monotherapy for those <15 years	One retrospective cohort study and three cross-sectional studies provided information on the age range of individuals included in their studies. • One retrospective cohort study (Allen et al 2019) included adolescents and young adults, aged 13 to 20 years, receiving care for gender dysphoria in their study. The authors did not give any information about a minimum age requirement for oestrogen initiation. • One cross-sectional study (Grannis et al 2019) included youth, aged nine to 21 years, receiving care at a gender development clinic. The authors did not give any information about a minimum age requirement for oestrogen initiation. • One cross-sectional study (Kramer et al 2024) included adolescents and young adults, aged 12 to 24 years, seeking gender-affirming treatment. The authors did not give any information about a minimum age requirement for oestrogen initiation. • One cross-sectional study (Valentine et al 2022) included patients, aged >2 years, with a diagnosis of gender dysphoria and with at least one outpatient visit to a paediatric hospital. The authors did not give any information about a minimum age requirement for oestrogen initiation.
Monitoring arrangements	No evidence was identified regarding monitoring arrangements for CYP receiving feminising medicines.
Study exclusion criteria	No evidence was identified regarding study exclusion criteria. One retrospective cohort study and three cross-sectional studies provided inclusion criteria. • One retrospective cohort study (Allen et al 2019) did not report on exclusion criteria. Inclusion criteria were adolescents and young adults, aged 13 to 20, receiving care for gender dysphoria at the Gender Pathway Service between 2015 and 2018. Participants were included if they had received feminising medicines for at least three months and if they had baseline and follow-up data points. • One cross-sectional study (Grannis et al 2022) did not report on exclusion criteria. Inclusion criteria were transgender and non-binary youth, aged

[18] PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (cities not stated), Nationwide Children's Hospital (Columbus, Ohio), St. Louis Children's Hospital, and Seattle Children's Hospital

Outcome	Evidence statement
	nine to 21, receiving care at a gender development clinic between 2018 and 2022. • One cross-sectional study (Kramer et al 2024) did not report on exclusion criteria. Inclusion criteria were transgender and gender diverse adolescents and young adults, aged 12 to 24, seeking gender-affirming treatment between 2015 and 2018. • One cross-sectional study (Valentine et al 2022) did not report on exclusion criteria. Inclusion criteria were transgender and gender diverse youth aged >2 years at last visit with at least one outpatient visit from 2009 to 2019 at one of six paediatric hospitals included in a clinical research network in the USA.
Abbreviations CYP: children and young people; GD: gender dysphoria; USA: United States (of America)	

6. Discussion

This rapid evidence review (RER) examined the clinical effectiveness, safety and cost-effectiveness of feminising medicines, comprising oestrogen monotherapy, compared with one or a combination of psychological support or social transitioning to the desired gender or no intervention, for children and young people (CYP) with gender incongruence who identify as a female gender and wish a binary physical transition. The critical outcomes of interest were impact on gender incongruence, impact on mental health and impact on quality of life. The important outcomes of interest were feminising physical changes, psychosocial impact, fertility, feasibility of feminising genital surgery, cognitive outcomes, detransition after receipt of feminising medicines, regret after receipt of feminising medicines and safety.

Comparator evidence for the clinical effectiveness of feminising medicines in CYP with gender incongruence who identify as a female gender and wish a binary physical transition was available for the critical outcomes of impact on gender incongruence and impact on mental health and for safety outcomes. Non-comparator evidence was available for the critical outcomes of impact on mental health and impact on quality of life. No evidence was available for any of the important outcomes, for cost-effectiveness of feminising medicines in this population, or for subgroups. The comparator studies compared oestrogen monotherapy with no oestrogen monotherapy; no studies were found comparing oestrogen monotherapy to psychological support or social transitioning. The comparator studies were all observational; in many there were baseline differences between the groups being compared and some studies did not adjust for potential confounding factors in the analysis.

All the studies demonstrated indirectness related to either the population or intervention of interest for this rapid evidence review. Mixed populations that included both adults and adolescents were common; three of the studies included some participants who were aged over 18 years at the time of the start of oestrogen monotherapy (or of gender incongruence diagnosis in the control group) (Grannis et al 2023 included participants aged nine years to 21 years; Kramer et al 2024 included participants aged 12 to 24 years; and Allen et al 2019 included participants aged 13 to 20 years). These studies were downgraded for indirectness. In two of the included studies, the populations were gender diverse and included both gender binary and non-binary individuals. If the majority of the population was wishing to achieve a binary transition, the study was considered for inclusion and downgraded for indirectness.

In one of the included studies a small number of the intervention group received GnRH analogues as well as oestrogen, and in two of the included studies some of the comparator group received, or may have received, GnRH analogues and/or spironolactone. None of the included studies reported any details about the oestrogen treatment regimes. One study

reported outcomes after a minimum of three months treatment (Allen et al 2019), and another reported a treatment duration of a median of 13.5 months (Grannis et al 2023). Two studies did not report treatment duration or the timing of outcomes measurement relative to the use of feminising medicines. The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions was not reported. Monitoring information was not reported in any of the included studies.

All of the evidence included in this RER comes from the United States. The patients in these studies were all attending gender clinics at private, paediatric hospitals. It is not clear if the individuals and aspects of care in the study reflect those seen in clinical practice in England and care is needed in generalising results to the NHS.

Two studies used electronic patient datasets to examine the effect of feminising medicines against critical outcomes of interest and safety outcomes. These databases use a mixture of codes to identify individuals diagnosed with gender incongruence who were prescribed feminising medicines, and their outcomes. The authors note that this method has high specificity, but lower sensitivity and it is possible that the population of persons with gender incongruence is underestimated. The underestimation may be greater in the population of individuals with gender incongruence not taking feminising medicines as they may not be accessing medical care for their gender incongruence and would not be identified in these datasets.

The number of individuals in each of the studies ranged from 14 participants in Allen et al (2019) to 349 participants in the intervention group and an unspecified number in the comparator group in Valentine et al (2022). One study had a total sample of 70 CYP AMAB, but reported outcomes on only a maximum of 53 individuals as data on hormone use was missing for some subjects.

The outcomes reported were primarily objective or assessed using standard assessment tools. The use of standardised outcome measures allows some interpretation of the level of burden associated with specific scores; however, it was not clear how clinically significant the changes observed were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

All outcomes reported were assessed as very low certainty evidence when evaluated using modified GRADE. Of particular note was the lack of reporting of psychological or psychosocial support / interventions in both the intervention and control populations; this increases the risk of bias through potential confounding. Limitations reducing the certainty of the outcomes included limited information about patient baseline demography and clinical

characteristics (Valentine et al 2022) and differences in baseline demography between groups (Grannis et al 2023); both of these increase selection bias. Three of the studies lacked identification or adjustment for potential confounding factors (Allen et al 2019, Grannis et al 2023 and Kramer et al 2024). Two studies were missing crucial information about the control population (Valentine et al 2022) or intervention (Kramer et al 2024). Furthermore, three of the included studies (Grannis et al 2023, Kramer et al 2024 and Valentine et al 2022), all of the studies with comparator evidence, were cross-sectional studies which limit the assessment of causality; since both the outcomes and the exposure (in this case oestrogen monotherapy) are measured at the same point in time, it is impossible to determine temporality, and these type of studies can only demonstrate associations.

7. Conclusion

This RER included four studies comparing the clinical effectiveness of feminising medicines, comprising oestrogen monotherapy, to one or a combination of psychological support or social transitioning to the desired gender, or no intervention, for children and young people (CYP) with gender incongruence who identify as a female gender and wish a binary physical transition. Three studies provided comparator evidence, and one provided non-comparator evidence. Much of the evidence was indirect due to the inclusion of mixed populations or interventions which are out-of-scope for this RER. For example, some populations included adults or non-binary individuals, some of those receiving oestrogen monotherapy also received other feminising medicines and there was limited information about the feminising medicines received. Evidence was available for all the critical outcomes of interest and for safety but not for any of the important outcomes of interest or for cost-effectiveness or subgroups. The comparator studies compared oestrogen monotherapy with no oestrogen; no studies were found comparing oestrogen monotherapy to psychological support or social transitioning. All evidence was of very low certainty.

One analytical cross-sectional study provided evidence for impact on gender incongruence, reporting lower levels of body image dissatisfaction in those receiving feminising medicines (not statistically significant) compared to those receiving feminising medicines. The authors reported a statistically significant difference (but no indication of the effect size or direction) in the body image dissatisfaction score between those on oestrogen monotherapy compared to those on other feminising medicines and those not on any feminising medicines. The evidence around the impact of feminising medicines on mental health was mixed with one cross-sectional study reporting statistically significantly higher levels of depression, social anxiety and suicidality, but no statistically significant difference in levels of anxiety, in those treated with oestrogen monotherapy compared with those not receiving oestrogen. One cross-sectional study reported statistically significantly higher levels of objective binge eating but no statistically significant difference in other disordered eating symptoms in those receiving oestrogen compared with those not receiving oestrogen. A retrospective cohort study found a lower level of suicidality (not tested statistically) following treatment with oestrogen monotherapy. For the last critical outcome of interest, impact on quality of life, one retrospective cohort study found that reported well-being was improved after treatment with oestrogen monotherapy, but no statistical tests were reported.

No evidence was available for any important outcomes of interest: feminising physical changes, psychosocial functioning, fertility, feasibility of feminising surgery, cognitive outcomes, detransition following receipt of feminising medicines and regret after receipt of feminising medicines.

Safety was reported in one cross-sectional study. The study reported statistically significant increased odds of dyslipidaemia, hypertension and liver dysfunction in CYP with gender incongruence on oestrogen monotherapy, compared to individuals not on oestrogen, in unadjusted analyses. These results were no longer statistically significant after adjusting for confounding factors.

Limitations reducing the certainty of the outcomes included limited information about patient baseline demography and clinical characteristics and differences in baseline demography between groups; both of these increase selection bias. Three of the studies lacked identification of or adjustment for potential confounding factors. Two studies were missing crucial information about the control population or intervention.

Overall, there is very low certainty evidence with inconsistent results for the selected outcomes in CYP with gender incongruence who identify as a female gender and wish a binary physical transition receiving oestrogen monotherapy. There is also a lack of direct evidence due to the mixed populations and mixed interventions which further limits the conclusions that can be drawn. No conclusions can be drawn about cost-effectiveness as no evidence was identified. Published studies which allow conclusions to be drawn about the effectiveness of oestrogen monotherapy for this population are needed.

Appendix A PICO document

The review questions for this evidence review are:

1. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the clinical effectiveness of treatment with oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
2. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the short-term and long-term safety of oestrogen monotherapy with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
3. For CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition, what is the cost-effectiveness of oestrogen monotherapy with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition that may benefit more from treatment with oestrogen monotherapy than the wider population?
5. From the evidence selected:
    a) What were the criteria used by the research studies to define gender incongruence?
    b) What were the starting criteria, formulation, duration and dose of oestrogen monotherapy for those aged 16 years up to their 18th birthday?
    c) Did any children aged 15 years or younger receive oestrogen monotherapy for gender transition? If so, in what circumstances?
    d) What monitoring was in place for CYP with gender incongruence who identify as a female gender and wish to undergo a binary physical transition receiving oestrogen monotherapy?
    e) What were the exclusion criteria in the studies?

P –Population and Indication	Children and young people (up to their 18th birthday) who have gender incongruence as defined by the study and identify as a female gender and wish to undergo a binary physical transition. [Some terms used to describe this population include, but are not limited to, male to female (MTF; M2F), gender queer, transperson, transfeminine, transfemale, transfem, transwoman, transgender, transgendered, gender non-conforming, transexual, trans-sex, trans*, cross gender or cross-sex (alternate spellings may be considered).

	The term gender incongruence may also be referred to as, but is not limited to, gender dysphoria, gender identity disorder, gender dysfunction, gender diverse, gender questioning or transsexualism. 'Gender incongruence of childhood' is a diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11 characterised by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years (WHO, 2025). Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis. 'Gender incongruence of adolescence or adulthood' is a diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11. Gender incongruence is characterised by "a marked and persistent incongruence between an individual's experienced gender and the assigned sex". It is important to note that it has been moved out of the "Mental and behavioural disorders" chapter and into the "Conditions related to sexual health" chapter so that it is not perceived as a mental health disorder. It does not include references to dysphoria or dysfunction. Gender dysphoria, within the section of gender identity disorders, is the term used in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) (American Psychiatric Association, 2022). In the DSM-5-TR definition, gender dysphoria has to be associated with clinically significant distress or impairment of function. Gender dysphoria is the more commonly used term clinically and among research papers. It is also most likely to be familiar to the lay public since it has been used widely in mainstream and social media. It is a label that is used colloquially to describe feelings, as well as being a formal diagnosis.] The following subgroups of CYP with gender incongruence are of interest: • Peri-pubertal vs post-pubertal • The stated duration of gender incongruence is either less than 6 months, 6- 24 months, or more than 24 months at time of assessment and/or treatment • The age of onset of gender incongruence • The age of onset of puberty • The age/ Tanner stage at which treatment was initiated with oestrogen monotherapy • CYP with gender incongruence who have a preexisting diagnosis of neurodiversity • CYP with gender incongruence who have a preexisting diagnosis of a learning disability • CYP with gender incongruence with a history of severe enduring mental disorder including anxiety, depression (with

	or without a history of self-harm and suicidality), psychosis, personality disorder, and eating disorders
I – Intervention	Feminising medicines comprising oestrogen monotherapy. Individuals taking feminising medicines may also be receiving psychological or psychosocial support. [Feminising medicines may be referred to as gender affirming hormones, cross sex hormones, sex reassignment, sex change, sex transformation, sex hormones, gender reassignment, gender change, gender transformation or gender hormones. Oestrogen can be given as a patch, gel, spray, injection or a tablet. Examples include: oral estradiol and its salts including valerate and hemihydrate (Zumenon, Progynova, Elleste Solo, Bedol, Delestrogen); oestrogen gel (Sandrena, Oestrogel); oestradiol patch (Evorel, Estradot, Estraderm, Progynova TS patch, FemSeven patch); oestradiol spray (Lenzetto); injectable oestrogens (Depo-Estradiol, Delestrogen). Oestrogen may also be referred to as estrogen, oestradiol, estradiol, 17beta-estradiol, E2, E3, estriol, oestriol and ethinylestradiol. This list is not exhaustive. Individuals may also have experienced a period of time or process known as 'real-life experience' (RLE), sometimes historically called 'real-life test' (RLT) where they have lived full-time in their identified gender role in order to be eligible for feminising medicines. This PICO excludes individuals who are receiving or have received GnRH analogues for the indication of puberty suppression or gender affirmation.]
	One or a combination of: 1. Psychological and psychosocial support 2. Social transitioning to the gender with which the individual identifies **OR** 3. No intervention [Psychological and psychosocial support include cognitive behavioural therapy (CBT), Psychoanalytic and Psychodynamic therapies, Humanistic and Existential Therapies, Interpersonal and Relational Therapies, Trauma-Focused Therapies, Arts and Expressive Therapies, mindfulness and self-compassion, attachment-based family therapy, attachment therapy, psychoeducation, gender exploratory therapy, exploratory therapy. • Examples of Cognitive and Behavioural Therapies include: Cognitive Behavioural Therapy (CBT), Dialectical Behaviour Therapy (DBT), Acceptance and Commitment Therapy (ACT), Exposure Therapy, Behaviour Therapy Examples of Psychoanalytic and Psychodynamic Therapies include: Psychoanalysis, Psychodynamic Therapy, Intensive short-term dynamic psychotherapy (ISTDP), sensorimotor psychotherapy

C – Comparator(s)	• Examples of Humanistic and Existential Therapies include: Person-Centered Therapy (Carl Rogers), Gestalt Therapy, Existential Therapy • Examples of Interpersonal, Relational and Systemic Therapies include: Interpersonal Therapy (IPT), Couples Therapy, Family Therapy, Group Therapy, Narrative Therapy, Mentalisation-based Therapy, Dyadic Developmental Psychotherapy (DDP), Narrative exposure therapy • Examples of Trauma-Focused Therapies include: Eye Movement Desensitization and Reprocessing (EMDR), Trauma-Focused CBT (TF-CBT) • Examples of Mindfulness-Based Therapies include: Mindfulness-Based Stress Reduction (MBSR), Mindfulness-Based Cognitive Therapy (MBCT) • Examples of Arts and Expressive Therapies include: Art Therapy, Music Therapy, Drama Therapy, Play-based Therapy, Theraplay • Examples of Integrative and Holistic Therapies include: Integrative Therapy, integrative counselling • Examples of Specialised Therapies include: Compassion-Focused Therapy (CFT), Schema Therapy, Solution-Focused Brief Therapy (SFBT). Psychosocial support also includes: assessment, extended assessment, therapeutic assessment. These longer assessments allow exploration at a deeper level to seek understanding. Interventions can be delivered by psychological practitioners including Clinical and Counselling Psychologists, Psychotherapists, other healthcare professionals with additional training and supervision (e.g., specialist nurse or therapeutic social worker), trained facilitators or counsellors. Interventions can be delivered face to face or online, individually or in groups. Duration of intervention can range from a single session to having no fixed duration or number of sessions. No intervention may include individuals who actively choose not to take any interventions.]
O – Outcomes	**<u>Clinical Effectiveness</u>** *There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected.* *<u>Critical to decision-making:</u>* • **Impact on gender incongruence** *This outcome is important to patients because gender incongruence is associated with significant distress and problems functioning.* [This outcome may be measured using the Utrecht Gender Dysphoria Scale (UGDS), Gender Dysphoria Questionnaire, Gender Identity Interview for Adolescents and Adults, Gender

	Identity Interview for Children, Gender Distress Scale (TYC-GDS), Self-reported satisfaction. Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Impact on mental health** *This outcome is important to patients because gender incongruence is associated with psychological distress which can lead to the development of mental health problems.* [Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, suicide, eating disorders, depression/low mood, anxiety, psychotic symptoms/psychosis, substance abuse, minority stress and trauma. This outcome may be measured using Child Behaviour Checklist (CBCL), Youth Self Report (YSR), Childhood Global Assessment Scale (CGAS), Revised Children's Anxiety and Depression Scale (and Subscales) (RCADS), The Child and Adolescent Psychiatric Assessment (CAPA), ED-15-Y eating disorder measure, Depression Anxiety Stress Scales (DASS-Y), Patient health questionnaire (PHQ-9) Modified for Teens, Beck Depression Inventory for Youth (BDI-Y), Beck Depression Inventory-II (BDI-II), Quick Inventory of Depressive Symptoms [QIDS], Generalised Anxiety Disorder Questionnaire (GAD-7), Hospital Anxiety and Depression Scale (HADS), Screen for Child Anxiety Related Emotional Disorders (SCARED), Ask Suicide Screening Questions (ASQ), Suicide Ideation Questionnaire Junior, Children's Rosenberg Self-Esteem Scale (CRSES), Clinical Outcomes in Routine Evaluation (CORE), Child Revised Impact of Events Scale 8 or 13 (CRIES 8 or 13), Dissociative Experiences Scale (DES), Assessment Checklist for Adolescents (ACA), Assessment Checklist for Children (ACC). Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Impact on Quality of Life** *This outcome is important to patients because gender incongruence may be associated with a significant reduction in health-related quality of life.* [Quality of life can be measured using a recognised quality of life score for example KINDL questionnaire, Kidscreen 10/27/52, Pediatric Quality of Life Inventory (PedsQL), EuroQuality of Life Five Dimensions Youth (EQ-5D-Y/EQ-5D-3L/EQ-5D-5L), Satisfaction with Life Scale for Children (SWLS-C), Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF), General Well-Being Scale (GWBS). Other measures (including self-reported) may be used as an alternative to the stated measures.] *<u>Important to decision making:</u>* • **Feminising physical changes** *This outcome is important because most patients with gender incongruence wish to take steps to suppress features of their*

	physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender. [Feminising physical changes can include: facial/body/head hair, breast growth, body fat and muscle distribution, erectile dysfunction, testicular size and function and voice change. Measures can include The Children's Body Image Scale (CBIS), Body Image Scale for Children (BISC), Body Dysmorphia scale YBOCS, Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder (BD D-YBO CS). Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Psychosocial impact** *This outcome is important to patients because gender incongruence is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning.* [Examples of psychosocial impact are coping mechanisms (such as substance misuse) which may impact on family relationships; peer relationships, living arrangements, educational attendance, work participation, romantic involvement, prosocial skills. Measures that may be used are The Work and Social Adjustment Scale – Youth versions (WSAS-Y), Strengths and Difficulties Questionnaire (SDQ), Multidimensional Scale of Perceived Social Support (MSPSS), Inventory of Interpersonal Problems (IIP32), Family Adaptability, Partnership, Growth, Affection and Resolve test. Other measures (including self-reported) may be used as an alternative to the stated measures.] • **Fertility** *This outcome is important to patients because feminising medicines can reduce fertility. Prior to commencing feminising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* [Examples of fertility outcomes include presence, number and quality of mature spermatozoa. Alternative measures may be used as reported in studies.] • **Feasibility of feminising genital surgery** *This outcome is important to patients because feminising medicines can have an impact on surgical outcomes. Treatments may alter the amount of genital tissue available for vaginoplasty, clitoroplasty and/or vulvoplasty.* • **Cognitive outcomes**

	This outcome is important to patients because feminising medicines can negatively impact cognitive processes such as concentration, memory, and executive function. [Observations and cognitive testing are performed by a trained professional which may include a key worker, support worker, social care, social worker or through school observations. This might include assessment of visuospatial ability, verbal memory, verbal fluency, verbal reasoning, verbal comprehension, visual memory, working memory, processing speed, computation, motor coordination, executive functioning, timed task completion or cognitive flexibility. Measures can include Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scale (WAIS), Adaptive Behaviours Assessment System (ABAS) or Wechsler Preschool and Primary Scale of Intelligence (WPPSI).] • **Detransition after receipt of feminising medicines** *Medical detransition is a complex experience encompassing medical, psychological, social implications and is important to patients because they may choose to discontinue treatment. The decision to detransition may or may not be associated with regret.* [Detransitioning is a concept that has evolved over time. Older studies may incorporate terminology relating to retransition. Relevant terms in the literature may include: detransitioner, desistence, discontinuation, cessation, termination, reversion, reversal, disidentification, reidentification.] • **Regret after receipt of feminising medicines** *This outcome is important to patients because some patients who choose to take feminising medicines may regret this decision. Regret may or may not be associated with detransition.* [This may be expressed as a proportion of the study population or other measures such as documentation of regret or semi-structured interviews.] **<u>Safety</u>** *It is important to assess whether treatment causes acute side effects that may lead to withdrawing the treatment or long-term effects that may impact on decisions for transitioning.* • Aspects to be reported could include: o Of most importance: Thromboembolic disease, cardiovascular disease, pre-diabetes (glycosylated haemoglobin (HbA1c) 42mmol/mol – 47mmol/mol, 6% vs 6.4%) or diabetes (HbA1c ≥48mmol/mol, ≥6.5%). o Breast cancer, impaired liver function, severe acne, gallstones, nausea, skin reactions and for those with diabetes, worsening control e.g. increase in HbA1c despite treatment or as defined in study.

	Cost effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	Up to 18 years
Date limits	2005-2025
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, PsycINFO and the Cochrane Library were searched limiting the search to papers published in English language in the last 20 years. Searches were not limited by hormone type (masculinising / feminising) or final transition goals (binary transition or non-binary transition); this was to ensure that the widest selection of papers were included in the search. Conference abstracts, non-systematic reviews, narrative reviews, case reports, commentaries, letters, editorials, guidelines and pre-prints were excluded.

Search dates: 01 January 2005 to 04 June 2025

1 adolescent/ or young adult/ or child/
2 adolescent health/ or child health/
3 Transition to Adult Care/
4 Pediatrics/
5 Puberty/
6 (child* or school* or p?ediatric* or adolescen* or preadolescen* or teen* or preteen* or young or youth? or girl? or boy? or puberty or pubescen*).ti,ab,kf.
7 or/1-6
8 Gender Dysphoria/
9 gender identity/ or transsexualism/
10 gender-nonconforming persons/ or transgender persons/
11 (gender adj2 (incongruen* or dysphoria* or dysfunction* or identit* or divers* or question*)).ti,ab,kf.
12 (trans or transgender* or transsex* or transperson* or transwom?n or transfem* or crossgender* or cross gender* or cross sex* or crosssex* or mtf or m2f or queer*).ti,ab,kf.
13 or/8-12
14 (femini?ing adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
15 ((gender* adj2 (affirm* or reassign* or re-assign* or transform* or transition* or chang*)) and (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
16 (gender adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
17 ((sex adj2 (affirm* or reassign* or re-assign* or transform* or transition* or chang*)) and (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
18 ((cross-sex adj hormon*) or (hormon* adj (therap* or treatment? or "use" or usage or supplement*))).ti,ab,kf.
19 Hormone Replacement Therapy/ or Estrogen Replacement Therapy/
20 Estrogens/tu
21 estradiol/tu
22 Ethinyl Estradiol/
23 (oestrogens or estrogens).ti,kf.
24 ((oestrogen? or estrogen?) adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or usage or supplement*)).ti,ab,kf.
25 ((oestrogen? or estrogen?) adj3 (oral* or buccal* or sublingual* or sub-lingual* or pellet? or implant* or patch* or spray* or gel? or cream? or dermal* or transdermal or subcutaneous or sub-cutaneous or inject* or intramuscular or intra-muscular)).ti,ab,kf.
26 (oestradiols or estradiols or ethinylestradiols or oestriols or estriols).ti,kf.

((oestradiol or estradiol or ethinylestradiol or oestriol or estriol) adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or
27 supplement*)).ti,ab,kf.
((oestradiol or estradiol or ethinylestradiol or oestriol or estriol) adj3 (oral* or buccal* or sublingual* or sub-lingual* or pellet? or implant* or patch* or spray* or gel? or cream? or dermal* or transdermal or subcutaneous or sub-cutaneous or inject* or
28 intramuscular or intra-muscular)).ti,ab,kf.
(zumenon or delestrogen* or sandrena or oestrogel or evorel or estradot or oestraderm or estraderm or progynova or ts patch* or femseven or fem seven or
29 lenzetto or estraor or Elleste Solo or Bedol).ti,ab,kf.
30 or/14-29
31 7 and 13 and 30
(animal or rat or rats or mice or mouse or murine or rodent? or cows or heifers or
32 sheep or ewes or goats or pigs or cats or dogs).ti.
33 31 not 32
34 limit 33 to (english language and yr="2005 -Current")
35 (comment or editorial or letter or preprint or review).pt. or case report.ti.
36 34 not 35
("systematic review" or scoping review).pt. or "Systematic Reviews as Topic"/ or ("Cochrane Database of Systematic Reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or (((((comprehensive or comprehensively) adj (analysis or review or reviewed)) or ((literature or scoping) adj (search or searches))).ti,ab,kf,kw. not "narrative review".ti.) and (database or databases or cinahl or cochrane or embase or psycinfo or pubmed or medline or scopus or (web adj1 science) or ((bibliographic or literature) adj (review or reviews)) or (((electronic adj (database or databases)) or (databases adj3 searched)) and (eligibility or excluded or exclusion or included or inclusion))).ti,ab,kf,kw.) or (((comparative adj effectiveness) and (effectiveness adj review)) or ((critical adj interpretive) and ((interpretive adj review) or (interpretive adj synthesis)))).ti,ab,kf,kw. or ((diagnostic adj test) and ((accuracy adj review) or (accuracy adj reviews) or (accuracy adj studies) or (accuracy adj study)) and (meta-analysis or scoping or systematic)).ti,ab,kf,kw. or ((evidence adj assessment) and GRADE).ti,ab,kf,kw. or ((evidence adj2 gap) and (gap adj map)).ti,ab,kf,kw. or ((evidence adj mapping) or (evidence adj review) or (exploratory adj review) or (framework adj synthesis) or (mapping adj review)).ti,ab,kf,kw. or ((meta adj (epidemiological or ethnographic or ethnography or interpretation or narrative or review or study or synthesis or summary or theory)) or metaethnographic or metaethnography or metasynthesis).ti,ab,kf,kw. or ((methodological or methodology) adj1 review).ti,ab,kf,kw. or ((mixed adj methods) and (methods adj1 (review or synthesis))).ti,ab,kf,kw. or ((narrative adj1 synthesis) or (overview adj4 reviews) or ("PRISMA" adj4 (guideline or guidelines or preferred or reporting or requirements)) or (PRISMA adj "P")).ti,ab,kf,kw. or (((prognostic or psychometric) adj1 review) or ((qualitative adj (evidence or research)) and ((evidence or research) adj synthesis))).ti,ab,kf,kw. or (((rapid adj evidence) and (evidence adj assessment)) or (rapid adj realist) or (rapid adj2 (review or reviews)) or (realist adj2 (review or reviews or syntheses or synthesis))).ti,ab,kf,kw. or (((review adj economic) and (economic adj1 (evaluation or evaluations))) or ((scoping or systematic) adj2 (review or reviews or studies or study))).ti,ab,kf,kw. or ((review adj1 reviews) or ((systematic adj evidence) and (evidence adj map)) or (systematic adj2 mapping) or (systematic adj2 literature) or (systematic adj2 (Embase or Medline or PsycInfo or PubMed)) or
37 (systematic adj2 (review or reviews)) or ((systematical or systematically) adj2

(review or reviewed reviews)) or (systematically adj identified) or (systematized adj review) or (umbrella adj (review or reviews))).ti,ab,kf,kw. or "Meta-Analysis".pt. or "meta-analysis as topic"/ or (meta adj2 (analyse or analyser or analyses or analysis or analytic or analytical or analytics or analyze or analyzed or analyzes)).ti,ab,kf,kw. or (metaanalyse or Metaanalysen or metaanalyser or metaanalyses or metaanalysis* or metaanalytic or metaanalytical or metaanalytics or metaanalyze or metaanalyzed or metaanalyzes).ti,ab,kf,kw. or "network meta-analysis"/ or (network adj1 (meta or metaanalyses or metaanalysis or metaregression)).ti,ab,kf,kw. or (systematic and ((meta adj regression) or metagression)).ti,ab,kf,kw.

38 34 and 37

39 36 or 38

40 Gender Dysphoria/

41 gender identity/ or transsexualism/

42 gender-nonconforming persons/ or transgender persons/

43 (gender adj2 (incongruen* or dysphoria* or dysfunction* or identit* or divers* or question*)).ti,ab,kf.

44 (trans or transgender* or transsex* or transperson* or transm?n or transmale? or transmasc* or crossgender* or cross gender* or cross sex* or crosssex* or ftm or f2m or queer*).ti,ab,kf.

45 or/40-44

46 (masculini?ing adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.

47 ((gender* adj2 (affirm* or reassign* or re-assign* or transform* or transition* or chang*)) and (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.

48 (gender adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.

49 ((sex adj2 (affirm* or reassign* or re-assign* or transform* or transition* or chang*)) and (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.

50 ((cross-sex adj hormon*) or (hormon* adj (therap* or treatment? or "use" or usage or supplement*))).ti,ab,kf.

51 Hormone Replacement Therapy/

52 exp Testosterone/tu

53 (testosterone adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or usage or supplement*)).ti,ab,kf.

54 (testosterone adj3 (capsule? or tablet? or oral* or buccal* or sublingual* or sub-lingual* or pellet? or implant* or patch* or spray* or gel? or cream? or dermal* or transdermal or subcutaneous or sub-cutaneous or inject* or intramuscular or intra-muscular)).ti,ab,kf.

55 (testosterone adj (isocaproate or undecanoate or enantate)).ti,ab,kf.

56 (tostran or testogel or testavan or sustanon or Testim or Delatestryl or Nebido or Roxadin or Aveed or Restandol Testocaps or Andriol testocaps or Jatenzo or Kyzatrex or Tlando).ti,ab,kf.

57 or/46-56

58 7 and 45 and 57

59 (animal or rat or rats or mice or mouse or murine or rodent? or cows or heifers or sheep or ewes or goats or pigs or cats or dogs).ti.

60 58 not 59

61 limit 60 to (english language and yr="2005 -Current")

62 (comment or editorial or letter or preprint or review).pt. or case report.ti.

63 61 not 62

64 ("systematic review" or scoping review).pt. or "Systematic Reviews as Topic"/ or ("Cochrane Database of Systematic Reviews" or evidence report technology

assessment or evidence report technology assessment summary).jn. or (((((comprehensive or comprehensively) adj (analysis or review or reviewed)) or ((literature or scoping) adj (search or searches))).ti,ab,kf,kw. not "narrative review".ti.) and (database or databases or cinahl or cochrane or embase or psycinfo or pubmed or medline or scopus or (web adj1 science) or ((bibliographic or literature) adj (review or reviews)) or (((electronic adj (database or databases)) or (databases adj3 searched)) and (eligibility or excluded or exclusion or included or inclusion))).ti,ab,kf,kw.) or (((comparative adj effectiveness) and (effectiveness adj review)) or ((critical adj interpretive) and ((interpretive adj review) or (interpretive adj synthesis)))).ti,ab,kf,kw. or ((diagnostic adj test) and ((accuracy adj review) or (accuracy adj reviews) or (accuracy adj studies) or (accuracy adj study)) and (meta-analysis or scoping or systematic)).ti,ab,kf,kw. or ((evidence adj assessment) and GRADE).ti,ab,kf,kw. or ((evidence adj2 gap) and (gap adj map)).ti,ab,kf,kw. or ((evidence adj mapping) or (evidence adj review) or (exploratory adj review) or (framework adj synthesis) or (mapping adj review)).ti,ab,kf,kw. or ((meta adj (epidemiological or ethnographic or ethnography or interpretation or narrative or review or study or synthesis or summary or theory)) or metaethnographic or metaethnography or metasynthesis).ti,ab,kf,kw. or ((methodological or methodology) adj1 review).ti,ab,kf,kw. or ((mixed adj methods) and (methods adj1 (review or synthesis))).ti,ab,kf,kw. or ((narrative adj1 synthesis) or (overview adj4 reviews) or ("PRISMA" adj4 (guideline or guidelines or preferred or reporting or requirements)) or (PRISMA adj "P")).ti,ab,kf,kw. or (((prognostic or psychometric) adj1 review) or ((qualitative adj (evidence or research)) and ((evidence or research) adj synthesis))).ti,ab,kf,kw. or (((rapid adj evidence) and (evidence adj assessment)) or (rapid adj realist) or (rapid adj2 (review or reviews)) or (realist adj2 (review or reviews or syntheses or synthesis))).ti,ab,kf,kw. or (((review adj economic) and (economic adj1 (evaluation or evaluations))) or ((scoping or systematic) adj2 (review or reviews or studies or study))).ti,ab,kf,kw. or ((review adj1 reviews) or ((systematic adj evidence) and (evidence adj map)) or (systematic adj2 mapping) or (systematic adj2 literature) or (systematic adj2 (Embase or Medline or PsycInfo or PubMed)) or (systematic adj2 (review or reviews)) or ((systematical or systematically) adj2 (review or reviewed reviews)) or (systematically adj identified) or (systematized adj review) or (umbrella adj (review or reviews))).ti,ab,kf,kw. or "Meta-Analysis".pt. or "meta-analysis as topic"/ or (meta adj2 (analyse or analyser or analyses or analysis or analytic or analytical or analytics or analyze or analyzed or analyzes)).ti,ab,kf,kw. or (metaanalyse or Metaanalysen or metaanalyser or metaanalyses or metaanalysis* or metaanalytic or metaanalytical or metaanalytics or metaanalyze or metaanalyzed or metaanalyzes).ti,ab,kf,kw. or "network meta-analysis"/ or (network adj1 (meta or metaanalyses or metaanalysis or metaregression)).ti,ab,kf,kw. or (systematic and ((meta adj regression) or metagression)).ti,ab,kf,kw.

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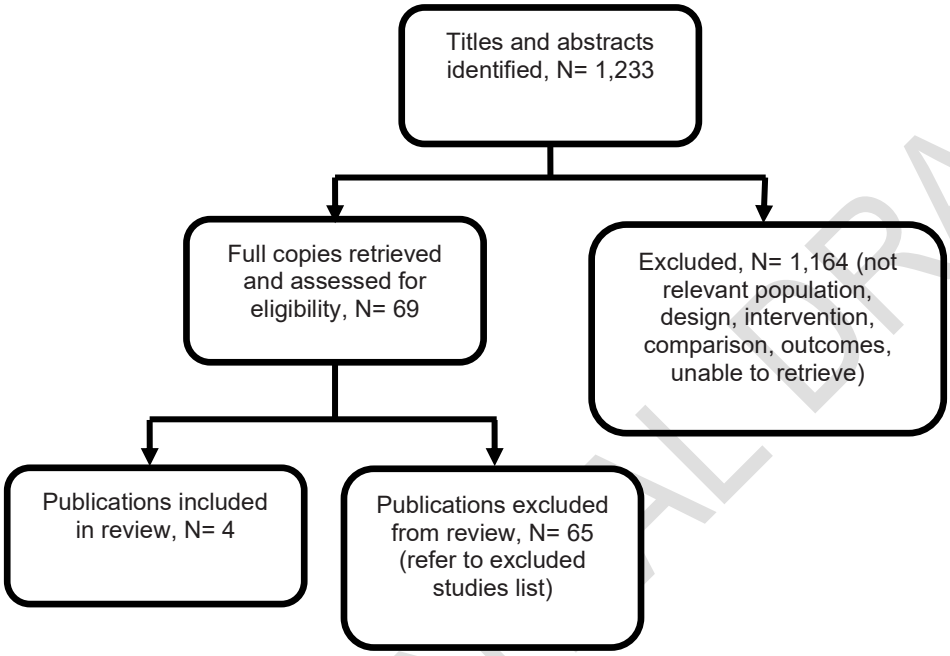
Appendix C Evidence selection

The literature searches identified 1,233 references. These were screened using their titles and abstracts and 69 references were obtained in full text and assessed for relevance. Of these, four references are included in the evidence summary. The remaining 65 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Not applicable.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aaron MS, Phulwani P. Single-Center Retrospective Analysis of Safety and Efficacy of Subcutaneous Estradiol Use in Transgender and Nonbinary Adolescents and Young Adults. Transgender Health. 2025.	Intervention out-of-scope (oestrogen + anti-androgens).
Avila JT, Golden NH, Aye T. Eating Disorder Screening in Transgender Youth. J Adolesc Health. 2019;65(6):815-7.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review. J. 2021;5(4):bvab011.	Intervention out-of-scope ("hormone therapy" which includes GnRH analogues + oestrogen). Outcomes presented as narrative summary with no meta-analysis; comparator mental health data available from primary studies.
Baram S, Myers SA, Yee S, Librach CL. Fertility preservation for transgender adolescents and young adults: a systematic review. Hum Reprod Update. 2019;25(6):694-716.	Population out-of-scope (mean age >18 years). Intervention out-of-scope (not oestrogen monotherapy).
Baskaran C, Roberts SA, Barrera E, Pilcher S, Kumar R. Venous thromboembolism in transgender and gender non-binary youth is rare and occurs in the setting of secondary risk factors: A retrospective cohort study. Pediatr Blood Cancer. 2024;71(11):e31284.	Intervention out-of-scope (single case on oestrogen + GnRH analogues, others on unknown gender-affirming hormone treatment).
Becker I, Auer M, Barkmann C, Fuss J, Moller B, Nieder TO, et al. A Cross-Sectional Multicenter Study of Multidimensional Body Image in Adolescents and Adults with Gender Dysphoria Before and After Transition-Related Medical Interventions. Arch Sex Behav. 2018;47(8):2335-47.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Becker-Hebly I, Fahrenkrug S, Campion F, Richter-Appelt H, Schulte-Markwort M, Barkmann C. Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: a descriptive study from the Hamburg Gender Identity Service. Eur Child Adolesc Psychiatry. 2021;30(11):1755-67.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Boogers LS, Wiepjes CM, Klink DT, Hellinga I, van Trotsenburg ASP, den Heijer M, et al. Transgender Girls Grow Tall: Adult Height Is Unaffected by GnRH Analogue and Estradiol Treatment. J Clin Endocrinol Metab. 2022;107(9):e3805-e15.	GnRH analogues used in the context of puberty suppression.

Study reference	Reason for exclusion
Borger O, Perl L, Yackobovitch-Gavan M, Sides R, Brener A, Segev-Becker A, et al. Body Composition and Metabolic Syndrome Components in Transgender/Gender Diverse Adolescents and Young Adults. LGBT health. 2024;11(5):359-69.	GnRH analogues used in the context of puberty suppression (100% of participants).
Boskey ER, Scheffey KL, Pilcher S, Barerra EP, McGregor K, Carswell JM, et al. A Retrospective Cohort Study of Transgender Adolescents' Gender-Affirming Hormone Discontinuation. J Adolesc Health. 2025;76(4):584-91.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (not oestrogen monotherapy).
Butler G, Adu-Gyamfi K, Clarkson K, El Khairi R, Kleczewski S, Roberts A, et al. Discharge outcome analysis of 1089 transgender young people referred to paediatric endocrine clinics in England 2008-2021. Arch Dis Child. 2022;107(11):1018-22.	GnRH analogues used in the context of puberty suppression.
Cantu AL, Moyer DN, Connelly KJ, Holley AL. Changes in Anxiety and Depression from Intake to First Follow-Up Among Transgender Youth in a Pediatric Endocrinology Clinic. Transgend Health. 2020;5(3):196-200.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Carrillo N, McGurran M, Melton BL, Moeller KE. Comparison of inpatient psychiatric medication management in gender diverse youth with cisgender peers. Ment. 2023;13(4):169-75.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Intervention out-of-scope (includes antiandrogens).
Chelliah P, Lau M, Kuper LE. Changes in Gender Dysphoria, Interpersonal Minority Stress, and Mental Health Among Transgender Youth After One Year of Hormone Therapy. J Adolesc Health. 2024;74(6):1106-11.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Includes both in-scope (GAH only) and out-of-scope interventions (GAH + GnRH analogues, GnRH analogues only, and menstrual suppression only) with no separate reporting of in-scope interventions.
Chen D, Abrams M, Clark L, Ehrensaft D, Tishelman AC, Chan YM, et al. Psychosocial Characteristics of Transgender Youth Seeking Gender-Affirming Medical Treatment: Baseline Findings From the Trans Youth Care Study. J Adolesc Health. 2021;68(6):1104-11.	No intervention (outcomes prior to feminising medicines).
Chen D, Berona J, Chan YM, Ehrensaft D, Garofalo R, Hidalgo MA, et al. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N Engl J Med. 2023;388(3):240-50.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.

Study reference	Reason for exclusion
Chew D, Anderson J, Williams K, May T, Pang K. Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics. 2018;141(4):04.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Chiniara LN, Bonifacio HJ, Palmert MR. Characteristics of Adolescents Referred to a Gender Clinic: Are Youth Seen Now Different from Those in Initial Reports? Horm Res Paediatr. 2018;89(6):434-41.	No intervention (outcomes prior to feminising medicines).
Crabtree L, Connelly KJ, Guerriero JT, Battison EAJ, Tiller-Ormord J, Sutherland SM, et al. A More Nuanced Story: Pediatric Gender-Affirming Healthcare is Associated With Satisfaction and Confidence. J Adolesc Health. 2024;75(5):772-9.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Dilday EA, Bukulmez O, Saner K, Lopez X, Jarin J. Sperm Cryopreservation Outcomes in Transgender Adolescents Compared with Adolescents Receiving Gonadotoxic Therapy. Transgend Health. 2022;7(6):528-32.	No intervention (outcomes prior to feminising medicines).
Dopp AR, Peipert A, Buss J, De Jesus-Romero R, Palmer K, Lorenzo-Luaces L. Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. Rand health q. 2025;12(2):2.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Feigerlova E. Prevalence of detransition in persons seeking gender-affirming hormonal treatments: a systematic review. J Sex Med. 2025;22(2):356-68.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Ginger A, Zwickl S, Angus LM, Leemaqz SY, Cook T, Wong AFQ, et al. Estradiol Concentrations and Wellbeing in Trans People Using Estradiol Hormone Therapy. Transgend Health. 2024;9(6):484-91.	Population out-of-scope (median age 37.5 years). Intervention out-of-scope (43% using progesterone, 55% using an anti-androgen); 32% had gender affirming surgery (out-of-scope for this RER).
Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. J Adolesc Health. 2022;70(4):643-9.	Includes both in-scope (people receiving feminising gender affirming hormone treatment - 8%) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Intervention out-of-scope (self-report of any treatment; regime not specified).

Study reference	Reason for exclusion
Gupta P, Patterson BC, Chu L, Gold S, Amos S, Yeung H, et al. Adherence to Gender Affirming Hormone Therapy in Transgender Adolescents and Adults: A Retrospective Cohort Study. J Clin Endocrinol Metab. 2023;108(11):e1236-e44.	Includes both in-scope (oestrogen only) and out-of-scope interventions (GnRH analogues prior to oestrogen in n=82/121) with no separate reporting of in-scope interventions.
Hannema SE, Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA. Efficacy and Safety of Pubertal Induction Using 17beta-Estradiol in Transgirls. J Clin Endocrinol Metab. 2017;102(7):2356-63.	GnRH analogues used in the context of puberty suppression.
Hisle-Gorman E, Schvey NA, Adirim TA, Rayne AK, Susi A, Roberts TA, et al. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. J Sex Med. 2021;18(8):1444-54.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Intervention out-of-scope (regime not specified).
Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. Headache. 2023;63(4):517-22.	GnRH analogues used in the context of puberty suppression (100% of participants).
Jarin J, Pine-Twaddell E, Trotman G, Stevens J, Conard LA, Tefera E, et al. Cross-Sex Hormones and Metabolic Parameters in Adolescents With Gender Dysphoria. Pediatrics. 2017;139(5).	Population out-of-scope (mean age 18 years). Intervention out-of-scope (includes antiandrogens + oestrogen, unknown number).
Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nord J Psychiatry. 2020;74(3):213-9.	No intervention (outcomes prior to feminising medicines).
Karalexi MA, Georgakis MK, Dimitriou NG, Vichos T, Katsimpris A, Petridou ET, et al. Gender-affirming hormone treatment and cognitive function in transgender young adults: a systematic review and meta-analysis. Psychoneuroendocrinology. 2020;119:104721.	Population out-of-scope (mean age 36.0 years). Intervention out-of-scope (oestrogen + anti-androgen). Note: this paper was included in 2417a (adult feminising, binary transition).
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	GnRH analogues used in the context of puberty suppression.
Knaus S, Steininger J, Klinger D, Riedl S. Body Mass Index Distributions and Obesity Prevalence in a Transgender Youth Cohort - A Retrospective Analysis. J Adolesc Health. 2024;75(1):127-32.	Intervention out-of-scope (regime not specified). No PICO specified outcomes.
Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics. 2020;145(4):04.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.

Study reference	Reason for exclusion
Lee MK, Yih Y, Willis DR, Fogel JM, Fortenberry JD. The impact of gender affirming medical care during adolescence on adult health outcomes among transgender and gender diverse individuals in the United States: The role of state-level policy stigma. LGBT health. 2024;11(2):111-21.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Ludvigsson JF, Adolfsson J, Hoistad M, Rydelius PA, Kristrom B, Landen M. A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. Acta Paediatr. 2023;112(11):2279-92.	GnRH analogues used in the context of puberty suppression.
MacKinnon KR, Jeyabalan T, Strang JF, Delgado-Ron JA, Lam JS, Gould WA, et al. Discontinuation of gender-affirming medical treatments: Prevalence and associated features in a nonprobabilistic sample of transgender and gender-diverse adolescents and young adults in Canada and the United States. J Adolesc Health. 2024;75(4):569-77.	GnRH analogues used in the context of puberty suppression. Population out-of-scope (mean age 21 years). Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Intervention out-of-scope (regime not specified).
Marwa A, Misra M, Lopez X. Determinants of Bone Mineral Density in Transgender Youth. Transgend Health. 2022;7(3):213-8.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (regime not specified).
McDeavitt K. Paediatric gender medicine: Longitudinal studies have not consistently shown improvement in depression or suicidality. Acta Paediatr. 2024;113(8):1757-71.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Interventions out-of-scope (not all individuals received oestrogen monotherapy).
McFarlane T, Zajac JD, Cheung AS. Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals-A systematic review. Clin Endocrinol (Oxf). 2018;89(6):700-11.	Population out-of-scope (mean age >18 years).
Miroshnychenko A, Ibrahim S, Roldan Y, Kulatunga-Moruzi C, Montante S, Couban R, et al. Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: a systematic review and meta-analysis. Arch Dis Child. 2025;110(6):437-45.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Mullins ES, Geer R, Metcalf M, Piccola J, Lane A, Conard LAE, et al. Thrombosis Risk in Transgender Adolescents Receiving Gender-Affirming Hormone Therapy. Pediatrics. 2021;147(4):04.	Population out-of-scope (mean age 18 years).

Study reference	Reason for exclusion
Nieder TO, Mayer TK, Hinz S, Fahrenkrug S, Herrmann L, Becker-Hebly I. Individual Treatment Progress Predicts Satisfaction With Transition-Related Care for Youth With Gender Dysphoria: A Prospective Clinical Cohort Study. J Sex Med. 2021;18(3):632-45.	Includes both in-scope (people receiving feminising gender affirming hormone treatment, n=4) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations. Intervention out-of-scope (regime not specified).
Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Juarez-Colunga E, et al. Body Composition and Markers of Cardiometabolic Health in Transgender Youth Compared With Cisgender Youth. J Clin Endocrinol Metab. 2020;105(3):01.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (n=4/14 were on a GnRH analogue and n=7/14 were on an antiandrogen, as well as oestrogen).
Nunes-Moreno M, Furniss A, Cortez S, Davis SM, Dowshen N, Kazak AE, et al. Mental Health Diagnoses and Suicidality Among Transgender Youth in Hospital Settings. LGBT health. 2025;12(1):20-8.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Nyquist CB, Torgersen L, David LW, Diseth TH, Gulbrandsen K, Waehre A. Treatment trajectories among children and adolescents referred to the Norwegian National Center for Gender Incongruence. Acta Paediatr. 2025;114(5):1006-14.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Oliphant J, Barnett D, Veale J, Denny S, Farrant B. The wellbeing and health needs of a cohort of transgender young people accessing specialist medical gender-affirming healthcare in Auckland. N Z Med J. 2021;134(1541):33-44.	No intervention (outcomes prior to feminising medicines).
Olson-Kennedy J, Okonta V, Clark LF, Belzer M. Physiologic Response to Gender-Affirming Hormones Among Transgender Youth. J Adolesc Health. 2018;62(4):397-401.	Population out-of-scope (mean age 18 years). Intervention out-of-scope (oestrogen + antiandrogen/GnRH analogue).
Olson-Kennedy J, Wang L, Wong CF, Chen D, Ehrensaft D, Hidalgo MA, et al. Emotional Health of Transgender Youth 24 Months After Initiating Gender-Affirming Hormone Therapy. J Adolesc Health. 2025;16:16.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Parikh N, Chattha A, Fredrickson JR, Walker D, Zhao Y, Gargollo P, et al. The Importance of Fertility Preservation in the Transgender Population. Urology. 2025;195:91-5.	No intervention (outcomes prior to feminising medicines).
Perl L, Brener A, Borger O, Segev-Becker A, Israeli G, Lebenthal Y, et al. The Role of Body Composition Assessment in Tailoring Gender-Affirming Treatment for Transgender/Gender Diverse Youth. Transgender Health. 2024.	GnRH analogues used in the context of puberty suppression.

Study reference	Reason for exclusion
Pham AH, Eadeh HM, Garrison MM, Ahrens KR. A Longitudinal Study on Disordered Eating in Transgender and Nonbinary Adolescents. Acad Pediatr. 2023;23(6):1247-51.	GnRH analogues used in the context of puberty suppression (100% of participants).
Prownpuntu T, Aungkawattanapong N, Subchartanan J, Suteerojntrakool O, Tempark T, Bongsebandhu-Phubhakdi C. Examining body image satisfaction among transfeminine and cisgender female youth in Thailand: a community-based survey. BMC Psychol. 2025;13(1):238.	Population out-of-scope (median age 19 years). Intervention out-of-scope (OTC contraceptives).
Reisner SL, Jadwin-Cakmak L, Sava L, Liu S, Harper GW. Situated Vulnerabilities, Sexual Risk, and Sexually Transmitted Infections' Diagnoses in a Sample of Transgender Youth in the United States. AIDS Patient Care STDS. 2019;33(3):120-30.	Population out-of-scope (median age 20.84 years). Intervention out-of-scope (not oestrogen monotherapy).
Roberts CM, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E. Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults. J Clin Endocrinol Metab. 2022;107(9):e3937-e43.	Population out-of-scope (>18 years). Intervention out-of-scope (regime not specified).
Segev-Becker A, Israeli G, Elkon-Tamir E, Perl L, Sekler O, Amir H, et al. Children and Adolescents with Gender Dysphoria in Israel: Increasing Referral and Fertility Preservation Rates. Endocr Pract. 2020;26(4):423-8.	No intervention (outcomes prior to feminising medicines).
Strang JF, Chen D, Nelson E, Leibowitz SF, Nahata L, Anthony LG, et al. Transgender Youth Executive Functioning: Relationships with Anxiety Symptoms, Autism Spectrum Disorder, and Gender-Affirming Medical Treatment Status. Child Psychiatry Hum Dev. 2022;53(6):1252-65.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Taylor J, Mitchell A, Hall R, Langton T, Fraser L, Hewitt CE. Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. Arch Dis Child. 2024;109(Suppl 2):s48-s56.	GnRH analogues used in the context of puberty suppression. Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Thompson L, Sarovic D, Wilson P, Irwin L, Visnitchi D, Samfjord A, et al. A PRISMA systematic review of adolescent gender dysphoria literature: 3) treatment. PLOS Glob Public Health. 2023;3(8):e0001478.	Intervention out-of-scope (no included studies reported oestrogen monotherapy).
Tollit MA, May T, Maloof T, Telfer MM, Chew D, Engel M, et al. The clinical profile of patients attending a large, Australian pediatric gender service: A 10-year review. Int J Transgend Health. 2023;24(1):59-69.	No intervention (outcomes prior to feminising medicines).

Study reference	Reason for exclusion
Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. JAMA netw. 2022;5(2):e220978.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE. 2022;17(1):e0261039.	Includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Correction: Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS ONE. 2023;18(6):e0287283.	Correction to excluded paper. Paper excluded as it includes both in-scope (people receiving feminising gender affirming hormone treatment) and out-of-scope population (people receiving masculinising gender affirming hormone treatment) with no separate reporting of in-scope populations.
Van Donge N, Schvey NA, Roberts TA, Klein DA. Transgender Dependent Adolescents in the U.S. Military Health Care System: Demographics, Treatments Sought, and Health Care Service Utilization. Mil Med. 2019;184(5-6):e447-e54.	GnRH analogues used in the context of puberty suppression. Intervention out-of-scope (n=3/13 on oestrogen).
Vehmas N, Holopainen E, Savolainen-Peltonen H. Metabolic and Anthropometric Changes and Adverse Effects in Finnish Adolescents Using Gender-Affirming Hormonal Treatment. Transgender Health. 2024.	Intervention out-of-scope (n=6/30 GnRH analogues + oestrogen; n=14 anti-androgen + oestrogen).

Abbreviations:

GAH: gender affirming hormones; GnRH: gonadotropin-releasing hormone; n: number; OTC: over the counter; PICO: population, intervention, comparison and outcome; RER: rapid evidence review

Appendix E Evidence table

The language used in this table is that of the study authors and may not reflect current language used by NHS England or NHS Gender Identity Services.

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. Clin. 2019;7(3):302-11. **Study location** USA (single centre) **Study type** Retrospective cohort study[19] **Study aim** To examine suicidality and general well-being following	**Inclusion criteria** Adolescents and young adults, aged 13-20 years, receiving care for gender dysphoria at Children's Mercy Hospital, Gender Pathway Service (GPS) clinic (Kansas City, Missouri) from 2015 to 2018. Participants were included if they had pretest and final assessment data points	**Interventions** GAH-only[21] GAH+GnRH analogue (GnRH analogues prior to GAH) **Comparators** None The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	Median (SD) duration of treatment, for the whole cohort, was 349 days (193 days). Median duration for those AMAB was not reported. **Critical outcomes** **Impact on mental health** *Suicidality*[22] mean (SE), n=14[23] • T_0 (prior to GAH): 1.21 (0.36) • T_1 (≥3 months after 1st dose of GAH): 0.24 (0.19) • p value: not reported **Impact on quality of life**	This study was appraised using the JBI checklist for case series. 1. Yes 2. Yes 3. Yes 4. No 5. No 6. Yes 7. No 8. No

[19] The comparator group for this study was out-of-scope for this RER (CYP with gender incongruence assigned female at birth (AFAB)) so the study has been appraised as a case series

[21] GAH-only was specified as participants that did not receive GnRH analogues prior to being administered GAH. No further details of exact medications supplied. The authors reported that the endocrinologists in their clinic sometimes begin participants at hormone levels lower than the recommended protocol, and typically, patients' doses are gradually increased every three to six months so that the dosage levels recommended by suggested protocols are reached by the end of treatment

[22] Suicidality was measured using the Ask Suicide-Screening Questions (ASQ). The ASQ is a four-item measure used to identify patients who are at risk of attempting suicide. Questions include: In the past few weeks have you… "…wished you were dead?", "…felt that you or your family would be better off if you were dead?", "…been having thoughts about harming or killing yourself?", or "…done anything to hurt yourself or to end your life?" The final question was modified from a lifetime risk of suicidality to risk of suicidality in the previous few weeks. Prior to 2017, the final question was not asked, and the score was imputed using expectation maximisation. A response of "no" was scored as 0 and a response of "yes" was scored as 1; with an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation

[23] n=14 AMAB participants: n=12 received GAH-only, n=2 received GAH+GnRH analogues. Results for CYP AMAB that received GAH-only were not presented separately

Study details	Population	Interventions	Study outcomes	Appraisal and funding
administration of gender-affirming hormones (GAH) **Study dates** 2015 to 2018	and were treated with GAH for at least 3 months. To access GAH and/or GnRH analogue treatment, a *"diagnosis of GD and a referral for medical treatment by a mental health professional is required."* **Exclusion Criteria** None stated **Total sample size** N=14 Assigned male at birth (AMAB) **No. of participants in each treatment group** AMAB GAH only: n=12 AMAB GAH+GnRH analogue: n=2 **Baseline characteristics**		*Well-being*[24] mean (SE), n=14 • T_0: 58.44 (4.09) • T_1: 69.52 (3.62) • p value: not reported	9. Yes 10. No **Other comments:** This paper reported a retrospective cohort study from a single, multi-disciplinary paediatric gender clinic in the USA. It has been appraised as a case series as individuals in the comparator group are out-of-scope for this RER. Individuals were included if they had a diagnosis for gender dysphoria and baseline and follow-up questionnaire data. It is unclear from the paper if all consecutive and eligible patients were included. Only the data for the participants assigned male at birth (AMAB) are presented here. The total number of participants AMAB included in the study was 14; 12 participants were prescribed gender affirming hormone therapy (GAH) only, whilst two participants were prescribed GAH with a GnRH analogue. The composition of the

[24] Well-being was measured using the PedsQL General Well-Being Scale (GWBS). The GWBS is a 5-point response scale, containing seven items, and measures "general well-being" and "general health". The general well-being subscale includes six items (eg "I feel happy" and "I think my health will be good in the future"). Participants are asked to consider each item over the past month and rate responses from 0 (never) to 4 (almost always). The general health subscale contains one item, "In general, how is your health?" ranging from 0 (Bad) to 4 (Excellent). All items are scored and linearly transformed to a 0 to 100 scale (initial score of 0 = 0, 1 = 25, 2 = 50, 3 = 75, and 4 = 100). Higher scores indicate perceptions of minimal problems, high wellbeing

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics were only presented for the full TGDY cohort and not reported separately for the AMAB population (N=47) Age (years) at administration of GAH, mean (range): 16.59[20] (13.73 to 19.04) Ethnicity, n (%): • White: 39 (83.0%) • Black: 1 (2.1%) • Asian: 1 (2.1%) • American Indian/ Alaska Native: 1 (2.1%) • Latinx/ Hispanic: 3 (6.4%) • Biracial/ multiracial: 2 (4.3%) Authors also reported ZIP code median income and insurance type.			feminising GAH treatment was not further defined. The inclusion criteria included all transgender persons, aged between 13 and 20 years, thus, it included both binary and nonbinary transgender individuals. The number of nonbinary individuals was not stated but they would be out-of-scope for this RER therefore the population indirectly relates to the population specified for this RER. Furthermore, individuals aged over 18 years at the time of GAH administration were out-of-scope for this RER. The authors stated that 90% of the sample was aged less than 18 years at date of first hormone dose and with a mean age at first administration of 16.59 years; the upper age limit for the whole sample was 19.04 years. The authors did not state the exact medications used for the AMAB GAH-only group, only that they did not include GnRH analogue and were oestrogen based. Two individuals AMAB had GAH with GnRH analogue and it is possible that others in the GAH-only group did not receive oestrogen

[20] This number differed from Table 1 and the text. The number here is that reported in the text

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				monotherapy. Both of these groups are out-of-scope for this RER; the cohort has been downgraded for indirectness due to intervention mis-match. No information was provided on any concurrent treatments. No information was provided regarding any psychological support or social transitioning prior to referral to the gender incongruence service. Outcomes were assessed using ASQ and PedsQL GWBS which are both standardised questionnaires used for evaluating mental health (suicide risk) and quality of life (general well-being). Transgender CYP not in contact with the service or without parental support would not be eligible for the service, so this may only include individuals already at a lower risk for poor mental health outcomes. Patients were also primarily white and from the mid-west USA, limiting generalisability to other transgender CYP populations. Statistical analyses explored the effect of missing data and heterogeneity. No potential confounders were identified or controlled for in ANCOVA analyses.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				P values were not reported for sub-analyses (AMAB and GAH-only groups). No subgroup analysis was reported. Individuals were treated at a private, multidisciplinary paediatric gender clinic in the United States. It is not clear how generalisable these findings might be to current NHS settings. **Source of funding:** None stated.
Grannis C, Mattson WI, Leibowitz SF, Nahata L, Chen D, Strang JF, et al. Expanding upon the relationship between gender-affirming hormone therapy, neural connectivity, mental health, and body image dissatisfaction. Psychoneuroendocrinology. 2023;156:106319. **Study location**	**Inclusion criteria** Transgender and non-binary (TNB) youth, aged 9-21 years, receiving care at a gender development clinic at a large children's hospital, (Columbus, Ohio) from 2018 to 2022. Participants must not have MRI contraindications (e.g.	**Interventions** Oestrogen monotherapy, in the form of transdermal patch or oral tablets[26] **Comparators** No oestrogen *n=10 AMAB in the no oestrogen group were receiving either GnRH analogues (in the form of puberty blockers) or spironolactone monotherapy	Mean (SD) duration of treatment was 13.53 months (8.69 months). **Critical outcomes** **Impact on gender incongruence** *Body Image Dissatisfaction*[27] mean (SD): oestrogen (n=15) vs no oestrogen (n=17); p value 85.33 (16.21) vs 88.53 (29.01); p value reported to be non-significant	This study was appraised using the JBI checklist for analytical cross-sectional studies. 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Unclear

[26] Medication information came from electronic medical records

[27] Body image dissatisfaction was measured to assess dysphoria related to various aspects of one's body; a specific screening tool was not detailed. Higher values indicate greater dissatisfaction with one's body image

Study details	Population	Interventions	Study outcomes	Appraisal and funding
USA (single centre) **Study type** Analytical cross-sectional **Study aim** To expand understanding of the role that gender-affirming hormone therapy (GAHT) has on internalising symptoms by examining both psychological and linked neural mechanisms of hormone treatment **Study dates** 2018 to 2022	braces, metal implants, etc). Participants were eligible for inclusion if they met "*diagnostic classification of gender dysphoria based on comprehensive mental health evaluation by a provider specialising in gender development.*" **Exclusion Criteria** None stated **Total sample size** N=32 AMAB **No. of participants in each treatment group** Oestrogen only: n=15 No oestrogen: n=17[25]	rather than no hormones at the time of data collection. The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	*Body Image Dissatisfaction,* oestrogen (n=15) vs other hormone therapy (n=10) vs no hormone therapy (n=7): effect size not presented, p=0.04 **Impact on mental health** *Screen for Child Anxiety Related Emotional Disorders (SCARED)*[28] mean (SD): oestrogen vs no oestrogen; p value 40.07 (20.17) vs 41.29 (15.19); p value reported to be non-significant *Children's Depression Inventory (CDI)*[29] mean (SD): oestrogen vs no oestrogen; p value 18.13 (8.13) vs 15.47 (7.14); p<0.05[30]	8. Yes **Other comments:** This paper reported a cross-sectional study from a single, multi-disciplinary paediatric gender clinic in the USA. Individuals were included if they had a diagnosis for gender dysphoria and were able to undergo MRI examination. Only the data for the participants assigned male at birth (AMAB) are presented here. The total number of participants AMAB included in the study was 324; 15 participants were prescribed oestrogen monotherapy, and 17 participants were included in the control group (no oestrogen therapy). The authors note, however, that 10 of the participants in the control group received either GnRH analogue (in the form of puberty blockers) or spironolactone

[25] n=10 participants in the no oestrogen group were receiving either GnRH analogues (in the form of puberty blockers) or spironolactone rather than no GAHT at the time of data collection
[28] The Screen for Child Anxiety Related Emotional Disorders (SCARED) is a self-completed questionnaire (with child/parent versions for those aged under 11 years), consisting of 41 items. Each question is graded on a scale of 0 – *"Not True or Hardly Ever True";* 1 – *"Somewhat True or Sometimes True"*; or 2 – *"Very True or Often True"*. A total score of ≥ 25 may indicate the presence of an anxiety disorder. Scores higher than 30 are more specific
[29] The Children's Depression Inventory (CDI) is a self-report questionnaire developed by Maria Kovacs to assess cognitive, affective, and behavioural signs of depression in children and adolescents, typically aged seven to 17. It consists of 27 items that are scored on a 0-2 scale, based on the statements *"…once in a while," "…many times,"* and *"…all the time,"*, to indicate the severity of symptoms over the past two weeks, focusing on areas like negative mood, self-esteem, and interpersonal problems. A higher total score on the CDI indicates a higher level of depressive symptoms
[30] Adjusted for age group

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics Age (years), mean (SD) • Oestrogen: 17.64 (0.86) • No oestrogen: 16.27 (1.49) • p<0.01 Ethnicity, n (%); oestrogen vs no oestrogen: • White: 13 (86.67%) vs 12 (70.59%%) • Black: 0 (0%) vs 1 (5.88%) • Asian: 1 (6.67%) vs 0 (0%) • American Indian/ Alaska Native: 0 (0%) vs 1 (5.88%) • Multiracial: 1 (6.67%) vs 1 (5.88%)		*Leibowitz Social Anxiety Scale (LSAS)*[31] mean (SD): oestrogen vs no oestrogen; p value 64.07 (38.62) vs 59.53 (32.94); p<0.05[32] *Suicidality*[33] mean (SD): oestrogen vs no oestrogen; p value 2.73 (1.83) vs 2.18 (1.38); p<0.05[34]	monotherapy rather than no hormones at the time of data collection. This sample is indirectly related to the control groups as defined by the PICO. The inclusion criteria included transgender persons wishing a binary physical transition, aged between nine and 21 years. Individuals identifying as non-binary were excluded from the analyses (AMAB: n=3) due to small numbers. Individuals aged over 18 years at the time of oestrogen administration were out-of-scope for this RER, thus the population is indirectly related to the PICO population of interest. No information was provided on any concurrent treatments. No information was provided regarding any psychological support or social transitioning prior to referral to the gender incongruence service. Outcomes were assessed using SCARED, CDI and LSAS which are

[31] The Liebowitz Social Anxiety Scale (LSAS) is a psychological assessment tool specifically designed to evaluate the range and severity of social anxiety disorder (SAD) symptoms. Respondents are asked to rate their level of fear or anxiety and the degree to which they avoid specific social and performance situations on a scale from 0 to 3, higher values indicate greater social anxiety

[32] Adjusted for age group

[33] Suicidality was measured by counting the frequency of suicidal ideation and/or attempts in the past year

[34] Adjusted for age group

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Authors also reported Hispanic/Latinx vs non-Hispanic/Latinx, and numbers of non-binary. Non-binary persons were excluded from analyses due to small numbers.			standardised questionnaires used for evaluating mental health (depression and anxiety). Two additional measures were used, that were not standardised measures, asking about the frequency and/or attempts of suicide in the previous year (mental health) and asking about satisfaction about one's body as a measure of gender dysphoria. Transgender CYP not in contact with the service or without parental support would not be eligible for the service, so this may only include individuals already at a lower risk for poor mental health outcomes. Patients were also primarily white and from the mid-west USA, limiting generalisability to other transgender CYP populations. Statistical analyses explored the effect of age and length of oestrogen treatment. Limited p values were presented for findings of interest. No subgroup analysis was reported. Individuals were treated at a private, multidisciplinary paediatric gender clinic in the United States. It is not clear how generalisable

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				these findings might be to current NHS settings. **Source of funding:** Support for the REDCap study is provided by a Vanderbilt Institute for Clinical and Translational Research grant from the National Institutes of Health (NIH). Funding was provided by internal funds from the Abigail Werner Research Institute at Nationwide Children's Hospital.
Kramer R, Aarnio-Peterson CM, Conard LA, Lenz KR, Matthews A. Eating disorder symptoms among transgender and gender diverse youth. Clin. 2024;29(1):30-44. **Study location** USA (single centre) **Study type** Cross-sectional (electronic register-based study) **Study aim**	**Inclusion criteria** Adolescents and young adults, aged 12-24 years, seeking gender-affirming treatment at a large paediatric medical center (Cincinnati, Ohio) from 2015 to 2018. Data were obtained through retrospective chart review of electronic health records.	**Interventions** Gender-affirming hormone (GAH)[36] **Comparators** No GAH The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	Median duration of treatment was not reported. **Critical outcomes** **Impact on mental health** *EDE-Q[37] ED Behaviours* n (%): GAH (n=14) vs no GAH (n=35 to 39 for different outcomes), p value • Subjective binge episode (n=50): 4 (28.6%) vs 8 (22.2%), p>0.05 • Objective binge episode (n=49): 7 (50.0%) vs 6 (17.1%), p=0.03	This study was appraised using the JBI checklist for analytical cross-sectional studies. 1. Yes 2. No 3. No 4. Unclear 5. No 6. Yes 7. Yes 8. Yes

[36] The authors do not specify the GAH used but state *"28% of TGD youth (n=53) reported prior use of gender-affirming hormones, including [o]estrogen (n=15) and testosterone (n=39)"*

[37] The Eating Disorder Examination-Questionnaire (EDE-Q) is a self-report questionnaire measuring disordered eating attitudes and behaviours over the past 28-days and is widely used. The Global EDE-Q score is an average of the four subscales (Restraint, Weight Concern, Shape Concern and Eating Concern) with individual EDE-Q items reflecting specific disordered eating behaviours (e.g. objective and subjective binge eating, laxative use, etc). Higher scores indicate more disordered eating; a score above 4 is indicative of a potential clinical ED

Study details	Population	Interventions	Study outcomes	Appraisal and funding
To 1) describe the frequency and severity of eating disorder (ED) symptoms in a sample of transgender and gender diverse (TGD) youth seeking gender-affirming treatment; 2) compare ED symptoms in transgender females and transgender males; and 3) examine the association between gender-affirming hormone use and ED symptoms in this cohort. **Study dates** January 2015 to September 2018	No details were provided regarding diagnosis of gender incongruence. **Exclusion Criteria** None stated **Total sample size** N=70 AMAB **No. of participants in each treatment group** Gender-affirming hormone use: n=14 No gender-affirming hormone use: n=unclear[35] **Baseline characteristics** Age (years), mean (SD): 17.79 (3.12) BMI (kg/m^2), mean (SD): 25.05 (6.49) Ethnicity, n (%): • White: 40 (90.9%) • Black: 3 (6.8%) • Asian: 1 (2.3%)		• Self-induced vomiting (n=49): 2 (14.3%) vs 3 (8.5%), p>0.05 • Laxative use (n=53): 3 (21.4%) vs 5 (12.8%), p>0.05 • Compensatory exercise (n=49): 4 (29.6%) vs 4 (11.4%), p>0.05 *Odds of objective binge eating (EDE-Q)* OR (95% CI); n=49: 4.83 (95% CI 1.23 to 18.98)	**Other comments:** This paper reported a cross-sectional study from a single, multi-disciplinary paediatric gender clinic in the USA. Individuals were included if they had a diagnosis for gender dysphoria and were seeking treatment at the gender clinic. Only the data for the participants AMAB are presented here. The total number of participants AMAB included in the study was 70; 14 participants were prescribed gender-affirming hormones; the number with no history of gender-affirming hormone use was not reported but between 35 and 39 subjects were included in the outcomes reported for this group. The authors note, however, that 63 participants (both AMAB and AFAB) were missing data on gender-affirming hormone use history (25% of sample). Furthermore, the authors did not specify the type of hormone therapy prescribed. It is noted that all feminising medicines beyond oestrogen monotherapy are out-of-scope for this RER, so the

[35] The authors note that data regarding use of gender-affirming hormone use was not available for n=63 of the total sample of TGD (including both AMAB and AFAB). It is not stated how many of those with unknown data are AMAB. Outcomes for AMAB with no GAH are reported for n of between 35 and 39.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Other: 0 (0%) Authors also reported Hispanic/non-Hispanic.			intervention is indirectly related to the PICO intervention of interest. The inclusion criteria included transgender persons wishing a binary physical transition, aged between 12 and 24 years. Individuals identifying as non-binary were excluded from the analyses (n=3) due to small numbers. Individuals aged over 18 years at the time of oestrogen administration were out-of-scope for this RER, thus the population is indirectly related to the PICO population of interest. No information was provided on any concurrent treatments. No information was provided regarding any psychological support or social transitioning prior to referral to the gender incongruence service. Outcomes were assessed using the EDE-Q standardised questionnaire and data from the questionnaire for specific ED behaviours. Transgender CYP not in contact with the service or without parental support would not be eligible for the service, so this may only include individuals already at a lower risk for poor mental health outcomes. Patients were also primarily white

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				and from the mid-west USA, limiting generalisability to other transgender CYP populations. Statistical analyses explored the effect of age, gender identity and BMI. Limited p-values were presented for findings of interest (only significance). Only statistically significant ORs were presented. No subgroup analysis was reported. Individuals were treated at a private, paediatric gender clinic in the United States. It is not clear how generalisable these findings might be to current NHS settings. **Source of funding:** The authors received no support for this research or publication and declared no conflicts of interest.
Valentine A, Davis S, Furniss A, Dowshen N, Kazak AE, Lewis C, et al. Multicenter Analysis of Cardiometabolic-related Diagnoses in Transgender and Gender-Diverse Youth: A PEDSnet Study. J Clin	**Inclusion criteria** Patients, aged over two years, entered on the Paediatric Learning Health System network with a diagnosis of gender dysphoria (or related diagnosis) and	**Interventions** Prescription for oestrogen without a GnRH analogue[39] **Comparators** TGDY without a prescription for GAHT	Duration of treatment not reported **Safety** *Odds of dyslipidaemia* • OR (95% CI), p value: 1.9 (1.3 to 2.7), p=0.001	This study was appraised using the JBI checklist for analytical cross-sectional studies. 1. Yes 2. No 3. Yes

[39] ATC or RxNorm codes were used to pull prescription information from the PEDSnet database: oestrogen (G03C, not including combined oral contraceptives, G03A)

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Endocrinol Metab. 2022;107(10):e4004-e14. **Study location** USA **Study type** Cross-sectional (multi-centre, electronic register-based study) **Study aim** 1) to evaluate the risk of diagnoses related to cardiometabolic health among transgender and gender diverse youth (TGDY) compared to matched controls, and 2) evaluate the potential association of various GAHTs on cardiometabolic-related diagnoses among TGDY **Study dates** 2009 to November 2019	at least one outpatient visit between 2009 and 2019 Transgender and gender diverse youth (TGDY) are defined in this study as *"having a diagnosis of gender dysphoria or related diagnosis (by PEDSnet concept ID…which include codes extracted from the EHR problem list or diagnosis code from any encounter)."* **Exclusion Criteria** None stated **Total sample size** N=1,407 AMAB **No. of participants in each treatment group** Oestrogen only: n=349	The use of other gender-affirming treatments such as surgery or psychological and psychosocial interventions were not reported.	• odds were not statistically significant following adjustment for confounders[40] *Odds of hypertension* • OR (95% CI), p value: 2.3 (1.7 to 3.2), p<0.0001 • odds were not statistically significant following adjustment for confounders *Odds of liver dysfunction* • OR (95% CI), p value: 1.6 (1.2 to 2.3), p<0.01 • odds were not significant following adjustment for confounders *Odds of hypertension* • OR (95% CI), p value: 2.3 (1.7 to 3.2), p<0.0001 • odds were not significant following adjustment for confounders	4. No 5. Yes 6. Yes 7. Yes 8. Yes **Other comments:** This paper reported a cross-sectional, registry-based analysis comparing cardiometabolic health in the US transgender adolescent population. The individuals included in this study were identified from a national paediatric health system database which includes data from a number of institutions[41] and is used for research purposes. Individuals were included if they had a diagnosis code for gender dysphoria from any encounter. Only the data for the participants taking oestrogen monotherapy are presented here. The total number of participants assigned male at birth included in the study was 1407; 349

[40] Analyses were adjusted for EHR recorded sex (sex assigned at birth), age at last visit, duration in PEDSnet, overweight/obesity status, depression and antipsychotic prescription

[41] PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. The PEDSnet system includes data from the following institutions: Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (cities not stated), Nationwide Children's Hospital (Columbus, Ohio), St Louis Children's Hospital and Seattle Children's Hospital

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	No gender affirming hormone treatment (GAHT): not clear[38] **Baseline characteristics** Baseline characteristics were only presented for the full TGDY cohort and not reported separately for the AMAB population Male in electronic health record (EHR) / assigned male at birth, n (%): 1,407 (33.7% of total cohort) Age (years) at first visit, median (IQR): 10.0 (4.4 to 14.6) Age (years) at last visit, median (IQR): 16.7 (14.6 to 18.3) Ethnicity, n (%): • White: 3,027 (72.5%) • Black: 257 (6.2%)			participants were prescribed oestrogen monotherapy. The inclusion criteria included all transgender persons, over the age of two years, thus, it included both binary and nonbinary transgender individuals. The number of nonbinary individuals was not stated but they would be out-of-scope for this RER therefore the population indirectly relates to the population specified for this RER. The number of individuals in the comparator group for these analyses was not stated. The authors state that some TGDY AMAB had a prescription for spironolactone (23.6%); however, they do not indicate if they were included in the analysis of those not on GAHT treatment. Likewise, 267 individuals (unknown assigned sex at birth) had a prescription for GnRH analogue alone; it is unclear if they were included in the control group. Both of these groups are out-of-scope for this RER. No information was provided on any concurrent treatments. No

[38] We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen only includes individuals who are AMAB only, but this is not explicitly stated in the paper

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	• Asian: 98 (2.3%) • Unknown: 401 (9.6%) • Other: 390 (9.3%) Total number of outpatient visits, median (IQR): 10 (4 to 26) Authors also reported Hispanic/non-Hispanic ethnicity, duration in PEDSnet, Site number and insurance type			information was provided regarding any psychological support or social transitioning prior to referral to the gender incongruence service. Outcomes were assessed using the electronic health register. Transgender persons not in contact with hospital or outpatient services would be excluded from the study. Persons with severe physical or mental illness who may not be eligible for gender affirming hormone treatment will also be excluded from the study. Missing data were not reported, and any attempts made to include missing data were not reported. The study controlled for sex assigned at birth, age at last visit, duration in PEDSnet, overweight/obesity status, depression and antipsychotic prescription in adjusted analyses. Confidence intervals and p values were both reported. No subgroup analysis was reported. Individuals were treated at private paediatric hospitals in the United States. It is not clear how

Study details	Population	Interventions	Study outcomes	Appraisal and funding
				generalisable these findings might be to current NHS settings. **Source of funding:** This work was supported by the National Institutes of Health / National Institute of Child Health and Human Development, the National Institutes of Health / National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the Doris Duke Foundation, the Pediatric Endocrine Society and the Society for Adolescent Health and Medicine. The funders had no role in the design or conduct of the study.

Abbreviations

AFAB: assigned female at birth; AMAB: assigned male at birth; ANCOVA: analysis of covariance; ASQ: Ask Suicide-Screening Questions; BMI: Body Mass Index; CDI: Children's Depression Inventory; CI: confidence interval; CYP: children and young people; E_2: oestrogen; ED: eating disorder; EDE-Q: Eating Disorder Examination-Questionnaire; EHR: electronic health record; GAH: gender affirming hormones; GAHT: gender affirming hormone therapy / gender affirming hormone treatment; GD: gender dysphoria; GnRH: gonadotropin-releasing hormone; GPS: Gender Pathway Service; GWBS: PedsQL General Well-Being Scale; IQR: interquartile range; kg: kilogram; m: metre; LSAS: Leibowitz Social Anxiety Score; MDT: multidisciplinary team; n: number; NHS: National Health Service; NIH: National Institutes of Health; OR: odds ratio; PCOS: polycystic ovary syndrome; PICO: population, intervention, comparison and outcome; RER: Rapid Evidence Review; SAD: Social Anxiety Disorder; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; SE: standard error; TGD: transgender and gender diverse; TGDY: transgender and gender diverse youth; TNB: transgender and non-binary; $T_{0:}$ pretest before administration of GAH; $T_{1:}$ after administration of GAH; USA: United States (of America); vs: versus

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

1. Were criteria for inclusion in the samples clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were the confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

The language used in this table is that of the study authors and may not reflect current language used by NHS England or NHS Gender Identity Services.

For abbreviations and footnotes see end of tables

Table 2. Oestrogen monotherapy compared to no intervention

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Oestrogen monotherapy	No GAHT	Result		
Impact on gender incongruence (1 cross-sectional study)									
Body image dissatisfaction[a], at mean (SD) duration of oestrogen monotherapy 13.53 months (8.69 months); mean (SD), p value (higher scores indicate greater dissatisfaction with one's body)									
1 cross-sectional study Grannis et al 2023	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	15	17[b]	mean (SD): oestrogen vs no oestrogen; p value 85.33 (16.21) vs 88.53 (29.01); p value reported to be non-significant	Critical	Very low
Body image dissatisfaction[a], at mean (SD) duration of oestrogen monotherapy 13.53 months (8.69 months); p value									
1 cross-sectional study Grannis et al 2023	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	15	Other hormone therapy (n=10) No hormone therapy (n=7)	effect size not presented; p=0.04	Critical	Very low
Impact on mental health (2 cross-sectional studies)									
Screen for Child Anxiety Related Emotional Disorders (SCARED)[c], at mean (SD) duration of oestrogen monotherapy 13.53 months (8.69 months); mean (SD), p value (higher scores indicate greater anxiety)									
1 cross-sectional study	Serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	15	17[b]	mean (SD): oestrogen vs no oestrogen; p value	Critical	Very low

Grannis et al 2023							40.07 (20.17) vs 41.29 (15.19); p value reported to be non-significant		
Children's Depression Inventory (CDI)[d], at mean (SD) duration of oestrogen monotherapy 13.53 months (8.69 months); mean (SD), p value (higher scores indicate a higher level of depressive symptoms)									
1 cross-sectional study Grannis et al 2023	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	15	17[b]	mean (SD): oestrogen vs no oestrogen; p value 18.13 (8.13) vs 15.47 (7.14); p<0.05[e]	Critical	Very low
Leibowitz Social Anxiety Scale (LSAS)[f], at mean (SD) duration of oestrogen monotherapy 13.53 months (8.69 months); mean (SD), p value (higher scores indicate greater social anxiety)									
1 cross-sectional study Grannis et al 2023	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	15	17[b]	mean (SD): oestrogen vs no oestrogen; p value 64.07 (38.62) vs 59.53 (32.94); p<0.05[e]	Critical	Very low
Suicidality[g], at mean (SD) duration of oestrogen monotherapy 13.53 months (8.69 months); mean (SD), p value (higher scores indicate greater suicidality)									
1 cross-sectional study Grannis et al 2023	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	15	17[b]	mean (SD): oestrogen vs no oestrogen; p value 2.73 (1.83) vs 2.18 (1.38); p<0.05[e]	Critical	Very low
Subjective binge episode, measured with EDE-Q[h], at mean duration of oestrogen monotherapy unknown; n (%), p value									
1 cross-sectional study Kramer et al 2024	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	14	36	GAH vs no GAH, p value: 4 (28.6%) vs 8 (22.2%), p>0.05	Critical	Very low
Objective binge episode, measured with EDE-Q[h], at mean duration of oestrogen monotherapy unknown; n (%), p value									
1 cross-sectional study Kramer et al 2024	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	14	35	GAH vs no GAH, p value: 7 (50.0%) vs 6 (17.1%), p=0.03	Critical	Very low

Odds of objective binge episode, measured with EDE-Q[h], at mean duration of oestrogen monotherapy unknown; OR (95% CI)									
1 cross-sectional study Kramer et al 2024	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Serious imprecision	14	35	4.83 (95% CI 1.23 to 18.98)	Critical	Very low
Self-induced vomiting, measured with EDE-Q[h], at mean duration of oestrogen monotherapy unknown; n (%), p value									
1 cross-sectional study Kramer et al 2024	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	14	35	GAH vs no GAH, p value: 2 (14.3%) vs 3 (8.5%), p>0.05	Critical	Very low
Laxative use, measured with EDE-Q[h], at mean duration of oestrogen monotherapy unknown; n (%), p value									
1 cross-sectional study Kramer et al 2024	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	14	39	GAH vs no GAH, p value: 3 (21.4%) vs 5 (12.8%), p>0.05	Critical	Very low
Compensatory exercise, measured with EDE-Q[h], at mean duration of oestrogen monotherapy unknown; n (%), p value									
1 cross-sectional study Kramer et al 2024	Very serious limitations[3]	Very serious indirectness[4]	Not applicable	Not calculable	14	35	GAH vs no GAH, p value: 4 (29.6%) vs 4 (11.4%), p>0.05	Critical	Very low
Safety (1 cross-sectional study)									
Odds of dyslipidaemia[i], at mean duration of oestrogen monotherapy unknown; OR (95% CI), p value									
1 cross-sectional study Valentine et al 2022	Serious limitations[6]	Very serious indirectness[7]	Not applicable	Not calculable	349	Unclear[j]	• OR (95% CI), p value: 1.9 (1.3 to 2.7), p=0.001 • odds were not statistically significant following adjustment for confounders[k]	Important	Very low
Odds of hypertension[i], at mean duration of oestrogen monotherapy unknown; OR (95% CI), p value									
1 cross-sectional study	Serious limitations[6]	Very serious indirectness[7]	Not applicable	Not calculable	349	Unclear[j]	• OR (95% CI), p value: 2.3 (1.7 to 3.2), p<0.0001	Important	Very low

Valentine et al 2022							• odds were not statistically significant following adjustment for confounders[k]		
Odds of liver dysfunction[i], at mean duration of oestrogen monotherapy unknown; OR (95% CI), p value									
1 cross-sectional study Valentine et al 2022	Serious limitations[6]	Very serious indirectness[7]	Not applicable	Not calculable	349	Unclear[j]	• OR (95% CI), p value: 1.6 (1.2 to 2.3), p<0.01 • odds were not statistically significant following adjustment for confounders[k]	Important	Very low
Abbreviations AFAB: assigned female at birth; AMAB: assigned male at birth; CDI: Children's Depression Inventory; CI: confidence interval; EDE-Q: Eating Disorder Examination-Questionnaire; EHR: electronic health record; GAH: gender affirming hormones; GAHT: gender affirming hormone therapy / gender affirming hormone treatment; GnRH: gonadotropin-releasing hormone; LSAS: Leibowitz Social Anxiety Score; n: number; OR: odds ratio; RER: Rapid Evidence Review; SAD: Social Anxiety Disorder; SCARED: Screen for Child Anxiety Related Emotional Disorders; SD: standard deviation; vs: versus									

1. *Risk of bias: very serious limitations due to selection bias (groups were significantly different in some demographic characteristics, e.g. age), lack of identification of and adjustment for some potential confounding factors and potential reporting bias (due to use of non-standardised questionnaires)*
2. *Indirectness: very serious indirectness as the population included individuals aged over 18 years (individuals aged 9 to 21 years were included) and the comparator included n=10/17 participants that received either GnRH analogues (in the form of puberty blockers) or spironolactone monotherapy (individuals receiving GnRHa in the form of puberty blockers are out-of-scope and those taking any form of feminising medicines are out-of-scope for the control group)*
3. *Risk of bias: very serious limitations due to measurement error (missing data on hormone administration for 25% of participants), lack of identification of and adjustment for potential confounding factors, and potential differences in standard treatment (no details of treatment or diagnoses defined by authors)*
4. *Indirectness: very serious indirectness as the population was adolescents and young adults, aged 12-24 years (individuals aged over 18 years are out-of-scope for this RER) and the intervention was gender affirming hormones (GAH), not specified (individuals receiving feminising medicines beyond oestrogen monotherapy were out-of-scope for this RER).*
5. *Imprecision: serious imprecision due to wide 95% confidence intervals that cross the default minimal clinically important difference lower threshold*
6. *Risk of bias: serious limitations due to not reporting baseline characteristics of in-scope individuals and not providing details on comparator group sample size and population*
7. *Indirectness: very serious indirectness as the population included individuals on the transfeminine spectrum, including feminine non-binary individuals and 24% of the population received the intervention spironolactone and 6.4% (of both AMAB and AFAB) had GnRH analogue prescriptions only, it is unclear if these individuals were in the analyses*

a. *Body image dissatisfaction was measured to assess dysphoria related to various aspects of one's body; a specific screening tool was not detailed. Higher values indicate greater dissatisfaction with one's body image*
b. *n=10 AMAB in the no GAHT group were receiving either GnRH analogues (in the form of puberty blockers) or spironolactone monotherapy rather than no treatment at the time of data collection*
c. *The Screen for Child Anxiety Related Emotional Disorders (SCARED) is a self-completed questionnaire (with child/parent versions for those aged under 11 years), consisting of 41 items. Each question is graded on a scale of 0 – "Not True or Hardly Ever True"; 1 – "Somewhat True or Sometimes True"; or 2 – "Very True or Often True". A total score of ≥ 25 may indicate the presence of an anxiety disorder. Scores higher than 30 are more specific*
d. *The Children's Depression Inventory (CDI) is a self-report questionnaire developed by Maria Kovacs to assess cognitive, affective, and behavioural signs of depression in children and adolescents, typically aged seven to 17. It consists of 27 items that are scored on a 0-2 scale, based on the statements "…once in a while," "…many times," and "…all the time,", to indicate the severity of symptoms over the past two weeks, focusing on areas like negative mood, self-esteem, and interpersonal problems. A higher total score on the CDI indicates a higher level of depressive symptoms*
e. *Adjusted for age group*

f. *The Liebowitz Social Anxiety Scale (LSAS) is a psychological assessment tool specifically designed to evaluate the range and severity of social anxiety disorder (SAD) symptoms. Respondents are asked to rate their level of fear or anxiety and the degree to which they avoid specific social and performance situations on a scale from 0 to 3, higher values indicate greater social anxiety*
g. *Suicidality was measured by counting the frequency of suicidal ideation and/or attempts in the past year*
h. *The Eating Disorder Examination-Questionnaire (EDE-Q) is a self-report questionnaire measuring disordered eating attitudes and behaviours over the past 28-days and is widely used. The Global EDE-Q score is an average of the four subscales (Restraint, Weight Concern, Shape Concern and Eating Concern) with individual EDE-Q items reflecting specific disordered eating behaviours (e.g. objective and subjective binge eating, laxative use, etc). Higher scores indicate more disordered eating; a score above 4 is indicative of a potential clinical ED*
i. *Outcomes were assessed using an electronic health register, collated for research purposes. PEDSnet is a Partner Network Clinical Data Research Network in the National Patient Centered Clinical Research Network, an initiative funded by the Patient Centered Outcomes Research Institute. PEDSnet institutions include the Children's Hospital Colorado, Children's Hospital of Philadelphia, Nemours Children's Health (cities not stated), Nationwide Children's Hospital (Columbus, Ohio), St. Louis Children's Hospital, and Seattle Children's Hospital*
j. *The paper reports the comparator group as TGDY never prescribed GAHT with no further details provided. We have assumed that the 'no GAHT' comparator group for individuals with a prescription for oestrogen includes only individuals who are AMAB, but this is not explicitly stated in the paper*
k. *Analyses were adjusted for EHR recorded sex (sex assigned at birth), age at last visit, duration in PEDSnet, overweight/obesity status, depression and antipsychotic prescription. Numerical results for adjusted analyses were not reported*

Table 3. Oestrogen monotherapy (no comparator)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Oestrogen monotherapy	Comparator	Result		
Impact on mental health (1 retrospective cohort study)									
Suicidality[a], at median (SD) duration of oestrogen monotherapy 349 days (193 days); mean (SE) (higher scores indicate greater suicidality)									
1 retrospective cohort study Allen et al 2019	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	14[b]	None	• T_0 (prior to GAH): 1.21 (0.36) • T_1 (≥3 months after 1st dose of GAH): 0.24 (0.19) • p value: not reported	Critical	Very low
Impact on quality of life (1 retrospective cohort study)									
Well-being[c], at median (SD) duration of oestrogen monotherapy 349 days (193 days); mean (SE) (higher scores indicate greater wellbeing)									
1 retrospective cohort study Allen et al 2019	Very serious limitations[1]	Very serious indirectness[2]	Not applicable	Not calculable	14[b]	None	• T_0 (prior to GAH): 58.44 (4.09) • T_1 (≥3 months after 1st dose of GAH): 69.52 (3.62) • p value: not reported	Critical	Very low

Abbreviations
AMAB: assigned male at birth; ASQ: Ask Suicide-Screening Questions; CYP: children and young people; GAH: gender affirming hormones; GnRH: gonadotropin-releasing hormone; GWBS: PedsQL General Well-Being Scale; n: number; RER: Rapid Evidence Review; SD: standard deviation; SE: standard error; T_0: pretest before administration of GAH; T_1: after administration of GAH; vs: versus

1. *Risk of bias: very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion), lack of identification of and adjustment for potential confounding factors and lack of summary statistic*
2. *Indirectness: very serious indirectness as the population was adolescents and young adults, aged 13-20 years, assigned male at birth (unclear how many wished a binary physical transition) (individuals aged over 18 years and identifying as non-binary or gender diverse are out-of-scope for this RER), there was no comparator group and the intervention was gender affirming hormones (GAH) without GnRH analogues for n=12 and GAH with GnRH analogues for n=2 (GAH not specified) (individuals receiving GnRH analogues were out-of-scope for this RER)*

a *Suicidality was measured using the Ask Suicide-Screening Questions (ASQ). The ASQ is a four-item measure used to identify patients who are at risk of attempting suicide. Questions include: In the past few weeks have you… "…wished you were dead?", "…felt that you or your family would be better off if you were dead?", "…been having thoughts about harming or killing yourself?", or "…done anything to hurt yourself or to end your life?" The final question was modified from a lifetime risk of suicidality to risk of suicidality in the previous few weeks. Prior to 2017, the final question was not asked, and the score was imputed using expectation maximisation. A response of "no" was scored as 0 and a response of "yes" was scored as 1; with an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation*

b. *n=14 AMAB participants: n=12 received GAH-only, n=2 received GAH+GnRH analogues. Results for CYP AMAB that received GAH-only were not presented separately*

c. *Well-being was measured using the PedsQL General Well-Being Scale (GWBS). The GWBS is a 5-point response scale, containing seven items, and measures "general well-being" and "general health". The general well-being subscale includes six items (eg "I feel happy" and "I think my health will be good in the future"). Participants are asked to consider each item over the past month and rate responses from 0 (never) to 4 (almost always). The general health subscale contains one item, "In general, how is your health?" ranging from 0 (Bad) to 4 (Excellent). All items are scored and linearly transformed to a 0 to 100 scale (initial score of 0 = 0, 1 = 25, 2 = 50, 3 = 75, and 4 = 100). Higher scores indicate perceptions of minimal problems, high wellbeing*

Glossary

Term	Definition[42]
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Child and/or young person	In law, everyone under 18 years of age is a child (Children Act 1989) but we recognise that it may be more appropriate to refer to those approaching the age of 18 as a young person, and that such young people may not recognise themselves as a “child”. In places, we have referred only to “young person”, or only to “child”, for example where treatment in question is only given towards the later stages of childhood, closer to the age of 18, or in reference to the parent/ child relationship, in which they remain the parents’ child, regardless of their age. Otherwise, we have used the phrase “child and/or young person” throughout the report for this reason only, and do not intend there to be a material difference between them other than that.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention. The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.
Cross-sectional study	A 'snapshot' observation of a set of people at 1 time. This type of study (sometimes called a cross-sectional survey) contrasts with a longitudinal study, which follows a set of people over a period of time.
Detransition/ detransitioners	The process of discontinuing or reversing a gender transition, often in connection with a change in how the individual identifies or conceptualises their sex or gender since initiating transition.

[42] These definitions are taken from the NICE glossary https://www.nice.org.uk/glossary and the glossary from the Cass Review [ARCHIVED CONTENT] Final Report – Cass Review

Term	Definition[42]
Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5)	The standard classification of mental disorders used by mental health professionals in the UK, and internationally, published by the American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5) is the latest version.
Feminising and masculinising hormones (also known as cross-sex hormones, and gender affirming hormones)	Sex hormones given as part of a medical transition for gender dysphoric individuals (testosterone for transgender males and oestrogen for transgender females).
Gender dysphoria	Diagnostic term used by health professionals and found in DSM-5 outlined above. Gender dysphoria describes “a marked incongruence between one’s experienced/ expressed gender and assigned gender of at least six months duration” which must be manifested by a number of criterion.
Gender identity	The developmental experience of a child or young person in seeking to understand their gender identity over time.
Gender incongruence	Diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11. Gender incongruence is characterised by “a marked and persistent incongruence between an individual’s experienced gender and the assigned sex”.
Gonadotropin releasing hormone analogues (also known as hormone blockers and puberty blockers) (GnRHa)	Taking these hormones stops the progress of puberty. The GnRH analogues (puberty blockers) act by competing with the body’s natural gonadotrophin releasing hormone. This competition blocks the release of two gonadotrophin hormones important in puberty called Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Non-binary	A gender identity that does not fit into the traditional gender binary of male and female.
Odds ratio	Compares the odds of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
Paediatrics	The branch of medicine dealing with children and their medical conditions.

Term	Definition[42]
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Psychosocial	Describes the psychological and social factors that encompass broader wellbeing.
Puberty blockers	See gonadotropin-releasing hormone analogues above.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Transgender / trans	This is an umbrella term that includes a range of people whose gender identity is different from the sex they were registered at birth.

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