NHS England Evidence Review:

Oestrogen monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation

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Oestrogen monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation

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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 oestrogen monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for children and young people (CYP) with gender incongruence who identify as non-binary and wish partial physical feminisation.

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. People seeking change consistent with non-binary expression of identity often have unique treatment goals that will require a flexible, individually-tailored approach. When deciding what medicines are appropriate for a non-binary trans feminine person it is important that the degree of fluidity of the person's current gender expression is assessed and a clear formulation of the mix of male, female, and neutral physical features is made.

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 gonadotrophin releasing hormone (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 the research studies to define gender incongruence, oestrogen monotherapy dosing, whether any CYP aged 15 years or younger received oestrogen monotherapy, monitoring arrangements and study exclusion criteria.

2. Executive summary of the review

This review examined the clinical effectiveness, safety and cost-effectiveness of oestrogen monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation. The searches for evidence published since 01 January 2005 were conducted on 17 June 2025 and identified 1245 references. These were screened using their titles and abstracts, and 78 full text papers were obtained and assessed for relevance against the criteria defined in the PICO for this review.

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 non-binary and wish partial physical feminisation’ 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.

No studies assessing the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation were identified for this review.

In terms of clinical effectiveness:

Critical outcomes

- No evidence was identified for the critical outcomes of impact on gender incongruence, impact on mental health and impact on quality of life.

Important outcomes

- No evidence was identified for the important outcomes of 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.

In terms of safety:

- No evidence was identified for short and long-term safety or adverse events.

In terms of cost-effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of CYP with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with oestrogen monotherapy than the wider population.

In terms of sub-questions

- As no relevant evidence was identified, it was not possible to answer the sub-questions about the criteria used by research studies to define gender incongruence, oestrogen dosing, whether any children aged 15 years or younger received oestrogen monotherapy, monitoring arrangements and study exclusion criteria.

Limitations

No evidence on the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation was identified.

Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation. 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 questions for this evidence review are:

1. For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, 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 non-binary gender or with no intervention?
2. For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, 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 non-binary gender or with no intervention?
3. For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, 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 non-binary gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as non-binary and wish partial physical feminisation 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 non-binary and wish partial physical feminisation 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 17 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 texts 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.

As no relevant studies were identified, the appendices for data extraction tables, critical appraisal checklists and GRADE profiles were not completed.

4. Summary of included studies

No studies assessing the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation were identified for this review.

5. Results

For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the clinical effectiveness and short-term and long-term safety of treatment with oestrogen monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender, or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender incongruence **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with significant distress and problems functioning.* **No evidence was identified for this outcome.**
Impact on mental health **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with psychological distress which can lead to the development of mental health problems.* **No evidence was identified for this outcome.**
Impact on quality of life **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence may be associated with a significant reduction in health-related quality of life.* **No evidence was identified for this outcome.**
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 supress 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 oestrogen can reduce fertility. Prior to commencing oestrogen, 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	*This outcome is important to patients because feminising medicines can have an impact on surgical outcomes as treatment may alter the amount of genital tissue available for vaginoplasty, clitoroplasty and/or vulvoplasty.*

Outcome	Evidence statement
Certainty of evidence: **Not** applicable	**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.* **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** Not applicable	**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.** **No evidence was identified for this outcome.**

For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the cost-effectiveness of oestrogen monotherapy compared to one or a combination of psychological support, social transitioning to the desired non-binary gender or no intervention?

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

From the evidence selected, are there particular subgroups of CYP with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with oestrogen monotherapy than the wider population?

Subgroup	Evidence statement
	No evidence was identified regarding any subgroups of CYP with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with oestrogen monotherapy than the wider population

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 treatment?**

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 CYPs with gender incongruence who identify as non-binary and wish partial physical feminisation receiving oestrogen monotherapy?**

e) **What were the exclusion criteria in the studies?**

	Evidence statement
Definitions of gender incongruence	No evidence was identified to address the sub-questions about the criteria used by research studies to define gender incongruence, oestrogen dosing, whether any children aged 15 years or younger received oestrogen monotherapy, monitoring arrangements and study exclusion criteria.
Oestrogen dosing	
Monitoring arrangements	
Study exclusion criteria	

6. Discussion

No evidence on the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation was identified.

Searches were conducted on five databases for studies published between 01 January 2005 and 17 June 2025. Study designs considered for inclusion included systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies and case series. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints, guidelines, case reports and resource utilisation studies were not eligible for inclusion.

7. Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy compared with one or a combination of psychological support or social transitioning to the desired non-binary gender or no intervention, for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation. 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 non-binary and wish partial physical feminisation, 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 non-binary gender or with no intervention?
2. For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, 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 non-binary gender or with no intervention?
3. For CYP with gender incongruence who identify as non-binary and wish partial physical feminisation, 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 non-binary gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of CYP with gender incongruence who identify as non-binary and wish partial physical feminisation 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 non-binary and wish partial physical feminisation 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 non-binary and wish partial physical feminisation. [Some terms used to describe this population include, but are not limited to, agender, gender fluid, non-binary transfeminine, transfem, genderqueer, polygender, gender diverse, gender non conforming, non-gender, transperson, transgender, transgendered, transexual, trans-sex, trans*, cross-gender, gender non conforming non binary (GNNB), trans-sex 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 oestradiol 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.]
C – Comparator(s)	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 • 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 • 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	**Clinical Effectiveness** *There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected.* *Critical to decision-making:* • **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 as treatment 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. **<u>Cost effectiveness</u>**
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, pre-prints, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, PsycINFO, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews were searched limiting the search to papers published in the English language in the last 20 years. Conference abstracts, non-systematic reviews, narrative reviews, case reports, commentaries, letters, editorials, guidelines, and pre-prints were excluded.

Search dates: 01 January 2005 to 17 June 2025.

Medline search strategy:

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	1 or 2 or 3 or 4 or 5 or 6
8	Gender-Nonconforming Persons/
9	((gender* adj3 (incongruen* or non-binary or nonbinary or non-conform* or nonconform* or divers* or ambig* or fluid* or fluctuat* or queer*)) or genderqueer or polygender* or poly-gender* or agender* or androgyne? or enby or gnnb or masculine wom?n or masculine female? or transfem* or feminine m?n or feminine male? or transmasc* or third gender or 3rd gender).ti,ab,kf. or transgender*.ti,kf.
10	(gender identity and (incongruen* or non-binary or nonbinary or non-conform* or nonconform* or divers* or ambig* or fluid* or fluctuat* or queer*)).ti,ab,kf.
11	8 or 9 or 10
12	((masculini?ing or femini?ing) adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
13	((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.
14	(gender adj2 (drug? or medicine? or medication? or agent? or hormone?)).ti,ab,kf.
15	((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.
16	Hormone Replacement Therapy/ or Estrogen Replacement Therapy/
17	Estrogens/tu
18	estradiol/tu
19	Ethinyl Estradiol/

20	(oestrogens or estrogens).ti,kf.
21	((oestrogen? or estrogen?) adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or usage or supplement*)).ti,ab,kf.
22	((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.
23	(oestradiols or estradiols or ethinylestradiols or oestriols or estriols).ti,kf.
24	((oestradiol or estradiol or ethinylestradiol or oestriol or estriol) adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or supplement*)).ti,ab,kf.
25	((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 intramuscular or intra-muscular)).ti,ab,kf.
26	(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 lenzetto or estraor or Elleste Solo or Bedol).ti,ab,kf.
27	Hormone Replacement Therapy/
28	exp Testosterone/tu
29	(testosterone adj3 (drug? or medicine? or medication? or agent? or therap* or treatment? or "use" or usage or supplement*)).ti,ab,kf.
30	(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.
31	(testosterone adj (isocaproate or undecanoate or enantate)).ti,ab,kf.
32	(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.
33	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34	7 and 11 and 33
35	(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.
36	34 not 35
37	limit 36 to (english language and yr="2005 -Current")
38	(comment or editorial or letter or preprint or review).pt. or case report.ti.
39	37 not 38
40	("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.

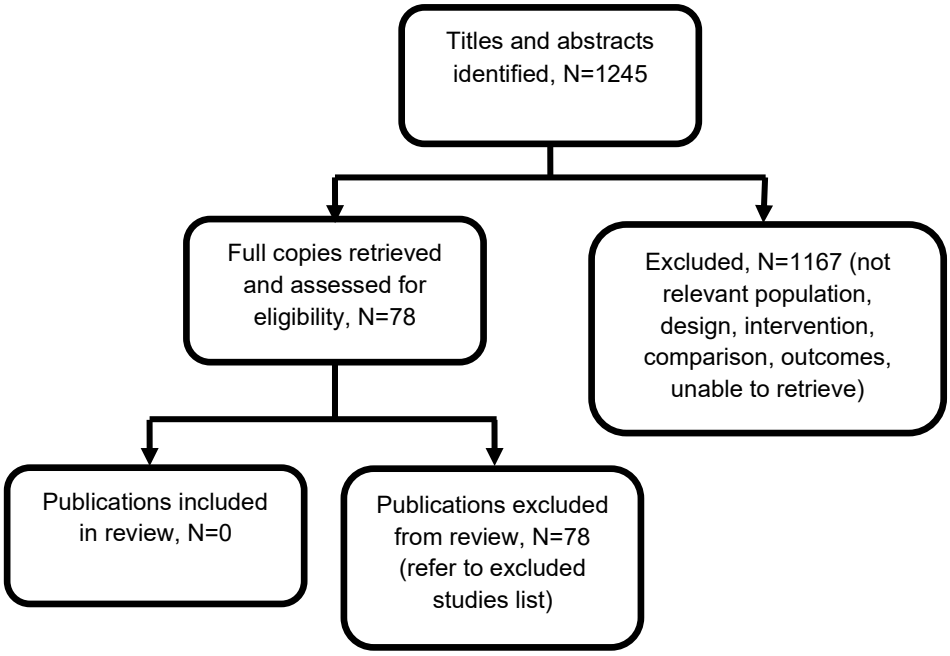
41 37 and 40

42 39 or 41

Appendix C Evidence selection

The literature searches identified 1,245 references. These were screened using their titles and abstracts and 78 full text papers were obtained and assessed for relevance against the criteria defined in the PICO for this review. Of these, 0 papers are included in the evidence summary. The remaining 78 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.	The population included 3 individuals who identified as non-binary; data not shown separately so population not in-scope.
Achille C, Taggart T, Eaton NR, Osipoff J, Tafuri K, Lane A, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. Int J Pediatr Endocrinol. 2020;2020:8.	Number of people identifying as non-binary not stated. Of the male-to-female individuals, 12% had no hormones and all the rest had puberty suppression, so none were on oestrogen monotherapy. Population and intervention not in-scope.
Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. Special Issue: Advancing the Practice of Pediatric Psychology With Transgender Youth. 2019;7(3):302-11.	The study did not make any distinction among participants for non-binary gender identities so population not in-scope.
Arcelus J, Claes L, Witcomb GL, Marshall E, Bouman WP. Risk Factors for Non-Suicidal Self-Injury Among Trans Youth. J Sex Med. 2016;13(3):402-12.	People identifying as non-binary (if any) not shown separately so population not in-scope.
Aungkawattanapong N, Prownpuntu T, Bongsebandhu-Phubhakdi C. Exploring Transfeminine Youth Health Disparities in Thailand: An Online Survey Analysis of Characteristics and Hormonal Use Patterns. Health Equity. 2024;8(1):676-82.	People identifying as non-binary (if any) not shown separately so population not in-scope.
Avila JT, Golden NH, Aye T. Eating Disorder Screening in Transgender Youth. J Adolesc Health. 2019;65(6):815-7.	People identifying as non-binary shown separately but none on oestrogen monotherapy so intervention not in-scope.
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.	Systematic review, no meta-analysis. Excluding the adult studies, the review included 1 non-binary youth but outcomes not reported separately so population not in-scope.
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.	Number of non-binary assigned male at birth (AMAB) population not reported and outcomes not reported separately for this group. 2 people who identified as non-binary were reported as having congenital thrombophilia; neither had VTE; both were assigned female at birth (AFAB).
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.	Gender grouping assumed a binary understanding of the division of gender into male (FtM) and female (MtF individuals) without considering possible non-binary identification so population not in-scope

Study reference	Reason for exclusion
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.	The study considered only individuals with gender dysphoria wishing a binary transition. There was no reference to non-binary individuals so population not in-scope.
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.	Results presented according to the individual's sex designated at birth; individuals identifying as non-binary not reported separately so population not in-scope.
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.	People identifying as non-binary reported separately for discontinuation of GAH but not stated how many on oestrogen monotherapy so intervention not in-scope.
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.	People identifying as non-binary not reported separately; not stated to have oestrogen monotherapy so population and intervention not in-scope.
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.	7 people with non-binary identities were included, but outcomes not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
Catlow C, Goffin S, Cunningham V, Abraham A, Grant C. The Health Needs and Management of Young People Accessing Paediatric Hauora Tahine (Transgender Health) Services in Te Tai Tokerau. J Paediatr Child Health. 2025;23:23.	People identifying as non-binary not shown separately by treatment group so population not in-scope.
Cavve BS, Bickendorf X, Ball J, Saunders LA, Thomas CS, Strauss P, et al. Reidentification With Birth-Registered Sex in a Western Australian Pediatric Gender Clinic Cohort. Jama, Pediatr. 2024;178(5):446-53.	People identifying as non-binary not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.

Study reference	Reason for exclusion
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.	People identifying as non-binary not shown separately so population not in-scope.
Chen D, Simons L, Johnson EK, Lockart BA, Finlayson C. Fertility Preservation for Transgender Adolescents. J Adolesc Health. 2017;61(1):120-3.	People identifying as non-binary not shown separately so population not in-scope.
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):1-18.	Systematic review, no meta-analysis. People identifying as non-binary not listed in any of the included studies or shown separately, so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
de Nie I, Asseler JD, Arnoldussen M, Baas S, de Vries ALC, Huirne JAF, et al. Reflecting on the Importance of Family Building and Fertility Preservation: Transgender People's Experiences with Starting Gender-Affirming Treatment as an Adolescent. Transgend Health. 2024;9(4):298-306.	People identifying as non-binary not shown separately so population not in-scope.
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.	Systematic review, no meta-analysis. Non-binary youth were either not reported or represented only a small subset of study participants. None of the included studies reported outcomes separately for non-binary individuals so population not in-scope.
Elkadi J, Chudleigh C, Maguire AM, Ambler GR, Scher S, Kozlowska K. Developmental Pathway Choices of Young People Presenting to a Gender Service with Gender Distress: A Prospective Follow-Up Study. Children (Basel). 2023;10(2):07.	The population included 1 individual identifying as non-binary but not on oestrogen monotherapy so intervention not in-scope.
Feigerlova E. Prevalence of detransition in persons seeking gender-affirming hormonal treatments: a systematic review. J Sex Med. 2025;22(2):356-68.	Systematic review, no meta-analysis. People identifying as non-binary not shown separately in any of the included studies so population not in-scope.
Gavidia R, Whitney DG, Hershner S, Selkie EM, Tauman R, Dunietz GL. Gender identity and transition: relationships with sleep disorders in US youth. J Clin Sleep Med. 2022;18(11):2553-9.	People identifying as non-binary not shown separately so population not in-scope.
Ginger A, Zwickl S, Angus LM, Leemaqz SY, Cook T, Wong AFQ, et al. Estradiol Concentrations and Wellbeing in Trans People	Population included 10 people identifying as non-binary (age range 16 to 75 years) but results not shown separately so population not in-scope.

Study reference	Reason for exclusion
Using Estradiol Hormone Therapy. Transgend Health. 2024;9(6):484	
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.	Numbers of individuals identifying as non-binary, or binary and non-binary, reported but outcomes not shown separately so population not in-scope.
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.	The population included 42 people identifying as non-binary in the 13-17 year age group on GAHT, but not stated if they were receiving oestrogen monotherapy and outcomes were not shown separately for this subgroup so population not in-scope.
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.	The authors stated that as the number of non-binary individuals was extremely small, they did not present the results separately for non-binary gender identities so population not in-scope.
Harrison DJ, Prada F, Nokoff NJ, Iwamoto SJ, Pastor T, Jacobsen RM, et al. Considerations for Gender-Affirming Hormonal and Surgical Care Among Transgender and Gender Diverse Adolescents and Adults With Congenital Heart Disease. J Am Heart Assoc. 2024;13(3):e031004.	Population included 4 people identifying as something other than transgender male or female (non-binary, gender fluid, etc.); outcomes not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
Hranilovich JA, Millington K. Headache prevalence in transgender and gender diverse youth: A single-center case-control study. Headache. 2023;63(4):517-22.	People identifying as non-binary not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
Karakilic Ozturan E, Ozturk AP, Bas F, Erdogdu AB, Kaptan S, Kardelen Al AD, et al. Endocrinological Approach to Adolescents with Gender Dysphoria: Experience of a Pediatric Endocrinology Department in a Tertiary Center in Turkey. J Clin Res Pediatr Endocrinol. 2023;15(3):276-84.	People identifying as non-binary not shown separately; not oestrogen monotherapy so population and intervention not in-scope.
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 with meta-analysis. Population is adults; authors state that gender non-binary or gender non-conforming individuals who do not identify as transgender are absent

Study reference	Reason for exclusion
systematic review and meta-analysis. Psychoneuroendocrinology. 2020;119:104721.	from to-date published literature; population not in-scope.
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	Population included 2 natal males who were described as 'undecided' but outcomes of feminising hormones not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	Population included three youth identified as non-binary, but they were excluded from analyses given low sample size so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
Lagrange C, Brunelle J, Poirier F, Pellerin H, Mendes N, Mamou G, et al. Clinical profiles and care of transgender children and adolescents in a specialized consultation in Ile-de-France. Neuropsychiatrie de l'Enfance et de l'Adolescence. 2023;71(5):270-80.	Population included 19 people identifying as non-binary; not stated how many had oestrogen monotherapy and outcomes not reported separately so population and intervention not in-scope
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.	People identifying as non-binary not shown separately so population not in-scope.
Lopez de Lara D, Perez Rodriguez O, Cuellar Flores I, Pedreira Masa JL, Campos-Munoz L, Cuesta Hernandez M, et al. Psychosocial assessment in transgender adolescents. An Pediatr (Engl Ed). 2020;93(1):41-8.	People identifying as non-binary not shown separately; not oestrogen monotherapy so population and intervention not in-scope.
Ma J, Ackley D, III, Reback CJ, Rusow JA, Skeen SJ, Miller-Perusse M, et al. Psychosocial correlates of gender-affirming hormone and medically necessary surgical intervention use among transgender and gender diverse youth and young adults. Psychology of Sexual Orientation and Gender Diversity. 2025:No Pagination Specified.	Only 1 person on hormones only aged 16-17 years; not stated if they identified as non-binary so population not in-scope.
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	Age 15 to 29; mean 21 years so population not in-scope.

Study reference	Reason for exclusion
Canada and the United States. J Adolesc Health. 2024;75(4):569-77.	
McCallion S, Smith S, Kyle H, Shaikh MG, Wilkinson G, Kyriakou A. An appraisal of current service delivery and future models of care for young people with gender dysphoria. Eur J Pediatr. 2021;180(9):2969-76.	People identifying as non-binary not shown separately so population not in-scope.
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.	Systematic review, no meta-analysis involving adults. One case reported of a person starting oestrogen at age <18 (age 16) but not stated to identify as non-binary so population not in-scope.
Millington K, Lee JY, Olson-Kennedy J, Garofalo R, Rosenthal SM, Chan YM. Laboratory Changes During Gender-Affirming Hormone Therapy in Transgender Adolescents. Pediatrics. 2024;153(5):01.	Population included 14 who identified as non-binary but outcomes not shown separately so population not in-scope.
Nahata L, Tishelman AC, Caltabellotta NM, Quinn GP. Low Fertility Preservation Utilization Among Transgender Youth. J Adolesc Health. 2017;61(1):40-4.	People identifying as non-binary not shown separately so population not in-scope.
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.	Population included 5 participants who identified with non-binary identities at follow-up (“in between," “non-binary," or “other"), but all were assigned female at birth and results were not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	Population included 20 people identifying as non-binary; they did not receive medical interventions so intervention not in-scope.
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.	Population included 4 people identifying as non-binary; none taking oestrogen so intervention not in-scope.

Study reference	Reason for exclusion
Olsavsky AL, Grannis C, Bricker J, Chelvakumar G, Indyk JA, Leibowitz SF, et al. Associations Among Gender-Affirming Hormonal Interventions, Social Support, and Transgender Adolescents' Mental Health. J Adolesc Health. 2023;72(6):860-8.	Population included 6 people identifying as non-binary; the authors state that they were unable to investigate the separate or additive roles of testosterone, oestrogen, and/or puberty blockers, or anti-androgens, for this group due to sample size constraints so population not in-scope.
Olson KR, Raber GF, Gallagher NM. Levels of Satisfaction and Regret With Gender-Affirming Medical Care in Adolescence. Jama, Pediatr. 2024;178(12):1354-61.	Population included 20 gender diverse (e.g. non-binary) individuals but not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	Includes 6 people (7%) non-binary or gender fluid but outcomes not shown separately so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
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.	Age range 16 to 24; mean 20.7 years so population not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
Roy MK, Bothwell S, Kelsey MM, Ma NS, Moreau KL, Nadeau KJ, et al. Bone Density in	People identifying as non-binary not shown separately so population not in-scope.

Study reference	Reason for exclusion
Transgender Youth on Gender-Affirming Hormone Therapy. J. 2024;8(5):bvae045.	
Sanchez-Toscano E, Dominguez-Riscart J, Larran-Escandon L, Mateo-Gavira I, Aguilar-Diosdado M. Cardiovascular Risk Factors in Transgender People after Gender-Affirming Hormone Therapy. J. 2023;12(19) (no pagination).	People identifying as non-binary not shown separately; not oestrogen monotherapy so population and intervention not in-scope.
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.	People identifying as non-binary not shown separately so population not in-scope.
Skorska MN, Saokhieo P, Thurston LT, Coome LA, Kaewthip O, Chariyalertsak S, et al. Exogenous Hormone Use Among Transfeminine Individuals in Chiang Mai, Thailand. Transgend Health. 2024;9(6):516-21.	People identifying as non-binary not shown separately so population not in-scope.
Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012;129(3):418-25.	People identifying as non-binary not shown separately so population not in-scope.
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.	A small minority (2 out of 124) endorsed a primarily non-binary gender identity (i.e., gender non-binary); results not shown separately so population not in-scope.
Tan KKH, Byrne JL, Treharne GJ, Veale JF. Unmet need for gender-affirming care as a social determinant of mental health inequities for transgender youth in Aotearoa/New Zealand. J Public Health (Oxf). 2023;45(2):e225-e33.	Age 14 to 26 years (mean 20.52 years); about half of the participants identified as non-binary but outcomes not shown for the 14 to 17 age group so population not in-scope.
Taylor J, Hall R, Langton T, Fraser L, Hewitt CE. Care pathways of children and adolescents referred to specialist gender services: a systematic review. Arch Dis Child. 2024;109(Suppl 2):s57-s64.	Systematic review, no meta-analysis. Outcomes for people identifying as non-binary not shown separately so population not in-scope.
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.	Systematic review, no meta-analysis. People identifying as non-binary not shown separately so population not in-scope.
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.	People who identified as non-binary not shown separately so population not in-scope.

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.	Population included 10 people who identified as non-binary, but outcomes for group on oestrogen only not shown separately so intervention not in-scope.
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.	Adults; 4 assigned male at birth who identified as gender queer or non-binary had had GAH at age 14 to 15 and 4 at age 16 to 17 but outcomes not shown for these groups separately so population not in-scope.
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 Endocrinol Metab. 2022;107(10):e4004-e14.	People who identified as non-binary not shown separately so population not in-scope.
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.	Population included 2 people assigned male at birth affirmed non-binary/undecided gender but number on oestrogen monotherapy not stated so intervention not in-scope.
Abbreviations: AFAB: assigned female at birth; AMAB: assigned male ta birth; GAHT: gender-affirming hormone treatment	

Appendix E Evidence table

No studies assessing the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation were identified for this review.

Appendix F Quality appraisal checklists

No checklists were used in this review.

Appendix G GRADE profiles

No studies assessing the clinical effectiveness, safety or cost-effectiveness of oestrogen monotherapy for CYP with gender incongruence who identify as non-binary and wish partial physical feminisation were identified for this review.

Glossary[1]

Term	Definition
Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether the event is suspected to be related to or caused by the drug, treatment or intervention.
Cognitive	Relating to, or involving, the process of thinking and reasoning.
Comparator	The standard (for example, another intervention or usual care) against which an intervention is compared in a study. The comparator can be no intervention (for example, best supportive care).
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.
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 (2013). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) was released in 2022.
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 (American Psychiatric Association 2013). Gender dysphoria describes *"a marked incongruence between one's experienced/ expressed gender and assigned gender of at least 6 months duration*" which must be manifested by a number of criteria.
Gender fluid	An experience of gender that is not fixed, but changes between two or more identities.
Gender identity	This term is used to describe an individual's internal sense of being male or female or something else.
Gender incongruence	Diagnostic term used by health professionals, found in the WHO International Classification of Diseases ICD-11 (see below). Gender incongruence is characterised by "*a marked and persistent incongruence between an individual's experienced gender and the assigned sex*".
Gender-questioning	A broad term used to describe CYP who are in a process of exploration about their gender.
Gender-related distress	A way of describing distress that may arise from a broad range of experiences connected to a child or young person's gender identity development. Often used for young people whereby any formal diagnosis of gender dysphoria has not yet been made.
Gonadotropin releasing hormone analogues (also known as hormone blockers and puberty blockers)	Taking these hormones stops the progress of puberty. The GnRH analogues (puberty blockers) act by competing with the body's natural gonadotrophin releasing hormones. This competition blocks the release of two gonadotropin hormones important in puberty called Follicular

[1] 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
	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.
International Classification of Diseases 11th Revision	The International Classification of Diseases (ICD) is a globally used medical classification of anything that is relevant to health care and is used clinically for medical diagnosis. (https://icd.who.int/en). It is developed and annually updated by the World Health Organisation (WHO) and is the mandatory global data standard for recording health information. It is currently in its 11th revision (ICD-11).
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.
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).
Psychosocial	Describes the psychological and social factors that encompass broader wellbeing.
Subgroup analysis	A way to find out from a study if a treatment is more effective in one group of people (for example, who are a particular age or have particular symptoms) than another. It uses evidence from a defined subgroup within the whole analysis set.
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.
Transition	These are the steps a person may take to live in the gender in which they identify. This may involve different things, such as changing elements of social presentation and role and/or medical intervention for some.

References

Included studies

No studies were included.

Other references

- American Psychiatric Association, DSM-5 Task Force. (2013). Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc.. https://doi.org/10.1176/appi.books.9780890425596
- American Psychiatric Association (2022). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR). https://doi/book/10.1176/appi.books.9780890425787
- World Health Organization. (2025). International statistical classification of diseases and related health problems (11th ed.). Available from: https://icd.who.int/.

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