NHS England Evidence Review:

Gonadotrophin-releasing hormone (GnRH) analogue monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation

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Gonadotrophin-releasing hormone (GnRH) analogue monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation

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Contents

1. Introduction 3
2. Executive summary of the review 5
3. Methodology 7
4. Summary of included studies 9
5. Results 10
6. Discussion 14
7. Conclusion 15
Appendix A PICO document 16
Appendix B Search strategy 24
Appendix C Evidence selection 27
Appendix D Excluded studies table 28
Appendix E Evidence table 32
Appendix F Quality appraisal checklists 33
Appendix G GRADE profiles 34
Glossary 35
References 37

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of gonadotrophin-releasing hormone (GnRH) analogue 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 no intervention, for children and young people 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.

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. Treatment also involves reducing the body's production of the male hormone testosterone, which decreases male physical appearance. Some individuals with a neutral gender identity may wish to have sex steroid production reduced using a GnRH analogue but not have oestrogen replacement. This evidence review focuses on these individuals.

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 children and young people within the included studies who might benefit from treatment with GnRH analogue monotherapy more than the wider population, the criteria used by research studies to define gender incongruence, GnRH analogue dosing regimens, circumstances in which any children and young people aged 15 years or younger received GnRH analogue monotherapy, monitoring arrangements and study exclusion criteria

2. Executive summary of the review

This review examined the clinical effectiveness, safety and cost-effectiveness of GnRH analogue 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 no intervention, for children and young people 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 03 July 2025 and identified 1,401 references. The titles and abstracts were screened, and 34 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 ‘children and young people 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 GnRH analogue monotherapy for children and young people 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 children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with GnRH analogue monotherapy than the wider population.

In terms of the sub-questions:

- As no evidence was identified, it was not possible to answer the sub-questions about the criteria used by research studies to define gender incongruence, GnRH analogue dosing regimens, the circumstances in which any children and young people aged 15 years or younger received GnRH, monitoring arrangements and study exclusion criteria

Limitations

No evidence on the clinical effectiveness, safety or cost-effectiveness of GnRH analogue monotherapy for children and young people 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 GnRH analogue 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 no intervention, for children and young people 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 GnRH analogue monotherapy for this population are needed.

3. Methodology

Review questions

The review questions for this evidence review are:

1. For children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the clinical effectiveness of treatment with GnRH analogue 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 no intervention?
2. For children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the short-term and long-term safety of treatment with GnRH analogue 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 no intervention?
3. For children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the cost-effectiveness of treatment with GnRH analogue 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 no intervention?
4. From the evidence selected, are there particular subgroups of children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with GnRH analogue 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 GnRH analogue monotherapy for those aged 16 years up to their 18th birthday?
    c) Did any children and young people aged 15 years or younger receive GnRH monotherapy for gender transition? If so, in what circumstances?
    d) What monitoring was in place for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation receiving GnRH analogue 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 03 July 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.

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 GnRH analogue monotherapy for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation were identified for this review.

5. Results

In children and young people 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 GnRH analogue 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 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 GnRH analogues can reduce fertility. Prior to commencing GnRH analogues patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* **No evidence was identified for this outcome.**

Outcome	Evidence statement
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 as treatment 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.* **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.**
Abbreviations GnRH: gonadotrophin-releasing hormone	

In children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the cost-effectiveness of treatment with GnRH analogue 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 no intervention?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for cost-effectiveness.**
Abbreviations GnRH: gonadotrophin-releasing hormone	

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

Subgroup	Evidence statement
	No evidence was identified regarding any subgroups of children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with GnRH analogue monotherapy than the wider population.
Abbreviations GnRH: gonadotrophin-releasing hormone	

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 GnRH analogue monotherapy for those aged 16 years up to their 18th birthday?
c) Did any children and young people aged 15 years or younger receive GnRH analogue monotherapy for gender transition? If so, in what circumstances?
d) What monitoring was in place for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation receiving GnRH analogue monotherapy?
e) What were the exclusion criteria in the studies?

Outcome	Evidence statement
Definitions of gender incongruence	
GnRH analogue dosing regimens	

Outcome	Evidence statement
Circumstances in which any children and young people aged 15 years or younger received GnRH	**No evidence was identified to address the sub-questions about the criteria used by research studies to define gender incongruence, GnRH analogue dosing, monitoring arrangements and study exclusion criteria.**
Monitoring arrangements	
Study exclusion criteria	
Abbreviations GnRH: gonadotrophin-releasing hormone	

6. Discussion

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

Searches were conducted on four databases for studies published between January 2005 and July 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 GnRH analogue 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 no intervention, for children and young people 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 GnRH analogue monotherapy for this population are needed.

Appendix A PICO document

The review questions for this evidence review are:

1. For children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the clinical effectiveness of treatment with GnRH analogue 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 children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the short-term and long-term safety of GnRH analogue 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 children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation, what is the cost-effectiveness of GnRH analogue monotherapy with or without psychological and psychosocial support compared to one or a combination of psychological support, social transitioning to the desired non-binary gender or with no intervention?
4. From the evidence selected, are there particular sub-groups of children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation that may benefit more from treatment with GnRH analogue 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 GnRH analogue monotherapy for those aged 16 years up to their 18th birthday?
    c) Did any CYP aged 15 years or younger receive GnRH monotherapy for gender transition? If so, in what circumstances?
    d) What monitoring was in place for children and young people with gender incongruence who identify as non-binary and wish partial physical feminisation receiving GnRH analogue 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 feminising medicines • 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	Gonadotrophin-releasing hormone (GnRH) analogue monotherapy. Individuals taking GnRH analogues may also be receiving psychological or psychosocial support. [GnRH analogues 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, LHRH analogues, LHRH agonists or gender hormones. Examples of GnRH analogues include: goserelin, triptorelin, leuprorelin, nafarelin, buserelin, gonadorelin. Goserelin is given subcutaneously, triptorelin and leuprorelin are given as subcutaneous or intramuscular injections, nafarelin is given as a nasal spray. Buserelin is given as nasal spray or subcutaneous injection. Gonadorelin is given via intravenous or subcutaneous injection. Any reference to GnRH analogues in the context of puberty suppression or used as puberty suppressing hormones must be excluded. In this context, GnRH analogues may also be described as, but are not limited to puberty blockers, puberty inhibitors or hormone blockers. 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 GnRH analogues. This PICO excludes individuals taking oestrogen monotherapy.]
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, 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 Congruence and Life Satisfaction (GCLS) total score, Gender dissonance severity scale (GDSS) or 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.]

	Important to decision making: • **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 GnRH analogues can reduce fertility. Prior to commencing GnRH analogues 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: o Reduced bone density, pancytopenia, thromboembolism, QT prolongation on ECG, pre-diabetes (glycosylated haemoglobin (HbA1c) 42mmol/mol – 47mmol/mol, 6% vs 6.4%) or diabetes (HbA1c ≥48mmol/mol, ≥6.5%). o Hot flushes, night sweats, headaches, muscle pain, reduced libido, jaundice, impaired liver function,

	inflammation of lungs or lung disease, nausea, vomiting, haemorrhage (bleeding), angioedema (e.g. swelling of part of the body), vision disorders, severe acne, seizure, hypertension 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 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 03 July 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	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	Gonadotropin-Releasing Hormone/tu
17	buserelin/ or goserelin/ or leuprolide/ or nafarelin/ or triptorelin pamoate/
18	(gonadotrophin releasing hormone? or gnrh or Luteinising hormone-releasing hormone? or lhrh).ti,ab,kf.
19	(buserelin or goserelin or leuprolide or nafarelin or triptorelin or gonadorelin).ti,ab,kf.

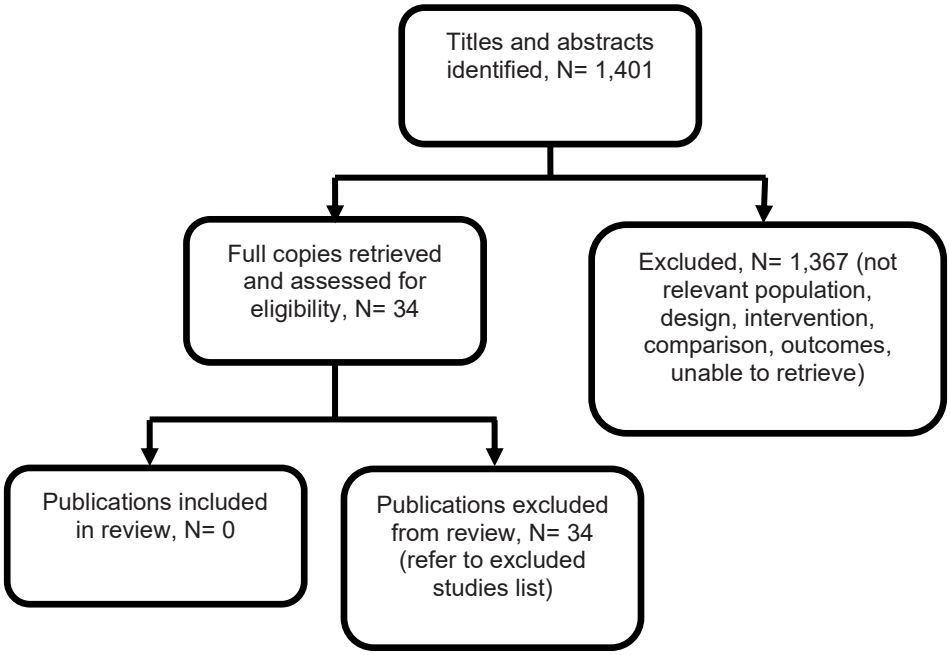
20 (lupron or eligard or zoladex or suprecur or suprefact or synarel or trelstar or decapeptyl or gonapeptyl or salvacyl).ti,ab,kf.
21 or/12-20
22 7 and 11 and 21
23 (animal or rat or rats or mice or mouse or murine or rodent? or cows or heifers or sheep or ewes or goats or pigs or cats or dogs).ti.
24 22 not 23
25 limit 24 to (english language and yr="2005 -Current")
26 (comment or editorial or letter or preprint or review).pt. or case report.ti.
27 25 not 26
28 ("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.
29	25 and 28
30	27 or 29

Appendix C Evidence selection

The literature searches identified 1,401 references. These were screened using their titles and abstracts and 34 references were obtained in full text and assessed for relevance. Of these, 0 references are included in the evidence summary. The remaining 34 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of antiandrogens and feminization in transgender women. Clin Endocrinol (Oxf). 2021;94(5):743-52.	Systematic review without meta-analysis. Population in all of the included studies received oestrogen. No studies were about treatment with GnRH analogues as monotherapy. Intervention out-of-scope
Boogers LS, van der Loos M, Wiepjes CM, van Trotsenburg ASP, den Heijer M, Hannema SE. The dose-dependent effect of estrogen on bone mineral density in trans girls. Eur. 2023;189(2):290-6.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-scope
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.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-scope
Brik T, Vrouenraets L, de Vries MC, Hannema SE. Trajectories of Adolescents Treated with Gonadotropin-Releasing Hormone Analogues for Gender Dysphoria. Arch Sex Behav. 2020;49(7):2611-8.	Context for the use of GnRH analogue monotherapy was puberty suppression. Text suggests that some of the population were children and young people who identified as non-binary but the proportion is not stated and no results are separately reported for this group. Population and intervention out-of-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.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
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.	Context for the use of GnRH analogue monotherapy was puberty suppression. Children and young people who identified as non-binary were a minority of the population (<10%) with no separate reporting for this group. Population and intervention out-of-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 without meta-analysis. Not clear that the studies included any children and young people who identify as non-binary. Not clear that the population were receiving GnRH analogues as monotherapy outside of the context of puberty suppression. Unable to match the systematic review to the PICO. Any individual potentially in-scope studies considered separately
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 without meta-analysis. Not clear that the population were receiving GnRH analogues as monotherapy outside of the context of puberty suppression. No separate/ pooled analysis of results for any children and young people who identify as non-binary. Unable to match the systematic review to the PICO. Any individual potentially in-scope studies considered separately
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 without meta-analysis. No separate/ pooled analysis of results for any children and young people who identify as non-binary receiving GnRH analogues as monotherapy. Any individual potentially in-scope studies considered separately

Study reference	Reason for exclusion
Fisher AD, Ristori J, Romani A, Cassioli E, Mazzoli F, Cocchetti C, et al. Back to the Future: Is GnRHa Treatment in Transgender and Gender Diverse Adolescents Only an Extended Evaluation Phase? J Clin Endocrinol Metab. 2024;109(6):1565-79.	Not clear that the population included any children and young people who identified as non-binary. Context for the use of GnRH analogue monotherapy was puberty suppression. Population and intervention out-of-scope
Gawlik A, Antosz A, Kasparek K, Nowak Z, Grabski B. Gender confirmation hormonal treatment use in young Polish transgender binary and non-binary persons. Endokrynol Pol. 2022;73(6):922-7.	None of the population received GnRH analogue monotherapy. Intervention out-of-scope
Jensen RK, Jensen JK, Simons LK, Chen D, Rosoklija I, Finlayson CA. Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgend Health. 2019;4(1):300-3.	Context for the use of GnRH analogue monotherapy not clear. Children and young people who identified as non-binary were excluded from the analysis. Population out-of-scope
Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. J Pediatr Endocrinol Metab. 2019;32(10):1077-81.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-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 and meta-analysis. Psychoneuroendocrinology. 2020;119:104721.	Systematic review with meta-analysis. Population in all of the included studies received oestrogen or testosterone. No studies were about treatment with GnRH analogues as monotherapy. Intervention out-of-scope
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	Context for the use of GnRH analogue monotherapy was puberty suppression. Children and young people who identified as non-binary were a minority of the population (2%) with no separate reporting for this group. Population and intervention out-of-scope
Klaver M, de Mutsert R, Wiepjes CM, Twisk JWR, den Heijer M, Rotteveel J, et al. Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. J Sex Med. 2018;15(2):251-60.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab. 2015;100(2):E270-5.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
Lavender R, Shaw S, Maninger JK, Butler G, Carruthers P, Carmichael P, et al. Impact of Hormone Treatment on Psychosocial Functioning in Gender-Diverse Young People. LGBT health. 2023;10(5):382-90.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
Masic U, Butler G, Carruthers P, Carmichael P. Trajectories of transgender adolescents referred for endocrine intervention in England. Arch Dis Child. 2022;107(11):1012-7.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
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	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people

Study reference	Reason for exclusion
with gender dysphoria. Eur J Pediatr. 2021;180(9):2969-76.	who identified as non-binary. Population and intervention out-of-scope
Nokoff NJ, Scarbro SL, Moreau KL, Zeitler P, Nadeau KJ, Reirden D, et al. Body composition and markers of cardiometabolic health in transgender youth on gonadotropin-releasing hormone agonists. Transgend Health. 2021;6(2):111-9.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
Norup PB, Haahr ME, Christiansen P, Aksglaede L, Cleemann L, Johannsen TH, et al. Growth and Adult Height Attainment in Danish Transgender Adolescents Treated With GnRH Analog and Sex Hormones. J Clin Endocrinol Metab. 2024;109(11):2764-73.	Not clear that the population included any children and young people who identified as non-binary. Context for the use of GnRH analogue monotherapy was puberty suppression. Population and intervention out-of-scope
Nos AL, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E, Susi A, et al. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. JAMA netw. 2022;5(11):e2239758.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-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.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
Perl L, Elkon-Tamir E, Segev-Becker A, Israeli G, Brener A, Oren A. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. J Pediatr Endocrinol Metab. 2021;34(6):741-5.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-scope
Roy MK, Bothwell S, Kelsey MM, Ma NS, Moreau KL, Nadeau KJ, et al. Bone Density in Transgender Youth on Gender-Affirming Hormone Therapy. J. 2024;8(5):bvae045.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. J Clin Endocrinol Metab. 2020;105(12):01.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-scope
Schulmeister C, Millington K, Kaufman M, Finlayson C, Kennedy JO, Garofalo R, et al. Growth in Transgender/Gender-Diverse Youth in the First Year of Treatment With Gonadotropin-Releasing Hormone Agonists. J Adolesc Health. 2022;70(1):108-13.	Context for the use of GnRH analogue monotherapy was puberty suppression. Children and young people who identified as non-binary were a minority of the population (<10%) with no separate reporting for this group. Population and intervention out-of-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.	Context for the use of GnRH analogue monotherapy not clear and no separate reporting of results for children and young people who received GnRH as monotherapy. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-scope
Steininger J, Knaus S, Kaufmann U, Ott J, Riedl S. Treatment trajectories of gender incongruent Austrian youth seeking gender-affirming hormone therapy. Front Endocrinol (Lausanne). 2024;15:1258495.	Context for the use of GnRH analogue monotherapy was puberty suppression. 3% of the population identified as non-binary with no separate reporting of outcomes for this group. Population and intervention out-of-scope

Study reference	Reason for exclusion
Tornese G, Di Mase R, Munarin J, Ciancia S, Santamaria F, Fava D, et al. Use of gonadotropin-releasing hormone agonists in transgender and gender diverse youth: a systematic review. Front Endocrinol (Lausanne). 2025;16:1555186.	Systematic review without meta-analysis. The intervention is stated as puberty suppression with or without additional gender affirming hormone treatment. Intervention out- of-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.	Context for the use of GnRH analogue monotherapy not clear. Not clear that the population included any children and young people who identified as non-binary. Population out-of-scope
van der Loos M, Klink DT, Hannema SE, Bruinsma S, Steensma TD, Kreukels BPC, et al. Children and adolescents in the Amsterdam Cohort of Gender Dysphoria: trends in diagnostic- and treatment trajectories during the first 20 years of the Dutch Protocol. J Sex Med. 2023;20(3):398-409.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out of scope
van der Loos MA, Hellinga I, Vlot MC, Klink DT, den Heijer M, Wiepjes CM. Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. J Bone Miner Res. 2021;36(5):931-41.	Context for the use of GnRH analogue monotherapy was puberty suppression. Not clear that the population included any children and young people who identified as non-binary. Population and intervention out-of-scope

Appendix E Evidence table

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

Glossary

Term	Definition[1]
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 children and young people 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 Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland.

[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[1]
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
- 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

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