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NHS England Evidence Review:

Masculinising medicines comprising testosterone with gonadotrophin-releasing hormone (GnRH) analogues for children and young people with gender incongruence who identify as non-binary and wish partial physical masculinisation

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Masculinising medicines comprising testosterone with gonadotrophin-releasing hormone (GnRH) analogues for children and young people with gender incongruence who identify as non-binary and wish partial physical masculinisation

Completed: January 2026

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 testosterone and gonadotrophin-releasing hormone (GnRH) analogues 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 (CYP) with gender incongruence who identify as non-binary and wish partial physical masculinisation.

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 masculine 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.

Masculinising medicines are used to help treat gender incongruence and make the patient's body more congruent with their gender identity. Treatment includes testosterone which can help develop more traditionally perceived masculine traits and reduce some of the typical feminine features of the body. Masculinising medicines are generally given lifelong and can used as monotherapy or alongside GnRH analogues. This evidence review focusses on testosterone given alongside GnRH analogues (not in the context of puberty suppression).

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 CYP within the included studies who might benefit from treatment with testosterone and GnRH analogues more than the wider population, the criteria used by research studies to define gender incongruence, testosterone/GnRH analogue dosing, circumstances in which any CYP aged 15 years or younger received testosterone with GnRH analogue therapy, monitoring arrangements and study exclusion criteria.

2. Executive summary of the review

This review examines the clinical effectiveness, safety, and cost-effectiveness of testosterone with GnRH analogues used as masculinising medicines (not for the indication of puberty suppression) 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, for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation.

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 masculinisation' rather than saying natal or biological sex and 'cross-sex hormones' are now referred to as 'masculinising or feminising medicines.' The data extracted from studies into Table 1, Appendix E: Evidence Table and Appendix G: GRADE profiles may use historical terms which are no longer considered appropriate.

The searches for evidence published since 01 January 2005 were conducted on 13 June 2025 and identified 1,495 references. The titles and abstracts were screened, and 25 full text papers were obtained and assessed for relevance against the criteria defined in the PICO for this review.

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

In terms of clinical effectiveness:

- No evidence was identified for the critical outcomes of impact on gender incongruence, impact on mental health and impact on quality of life.
- No evidence was identified for the important outcomes of masculinising physical changes, psychosocial impact, fertility, feasibility of masculinising genital surgery, cognitive outcomes, detransition after receipt of masculinising medicines and regret after receipt of masculinising medicines.

In terms of safety:

- No evidence was identified for safety.

In terms of cost effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- As no evidence was identified, it was not possible to identify particular sub-groups of CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation that may benefit more from treatment with testosterone with GnRH analogues than the wider population.

In terms of the subquestions:

- 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, testosterone dosing regimens, GnRH analogue dosing regimens, the circumstances in which any children and young people aged 15 years or younger received GnRH analogues, monitoring arrangements and study exclusion criteria.

Limitations

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

Conclusion

No evidence was identified that allowed any conclusions to be drawn about the clinical effectiveness, safety or cost-effectiveness of masculinising medicines comprising testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation. Published comparator studies about the effectiveness of testosterone with GnRH analogues for this population are needed.

3. Methodology

Review questions

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

1. For CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the clinical effectiveness of treatment with testosterone with GnRH analogues 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 masculinisation, what is the short-term and long-term safety of testosterone with GnRH analogues 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 masculinisation, what is the cost-effectiveness of testosterone with GnRH analogues 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 masculinisation that may benefit more from treatment with testosterone with GnRH analogues 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 testosterone for those aged 16 up to their 18th birthday?
    c) What were the starting criteria, formulation, duration and dose of GnRH analogue treatment for those aged 16 years up to their 18th birthday?
    d) Did any CYP aged 15 years or younger receive testosterone with GnRH analogues for gender transition? If so, in what circumstances?
    e) What monitoring was in place for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation receiving testosterone with GnRH analogues?

f) 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 13 June 2025.

See Appendix B for details of the search strategy.

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

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

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

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

4. Summary of included studies

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

5. Results

In CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the clinical effectiveness and safety of treatment with testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender incongruence **Certainty of evidence:** 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	
Masculinising physical changes **Certainty of evidence:** Not applicable	*This outcome is important because most patients with gender incongruence wish to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their experienced gender.* **No evidence was identified for this outcome.**
Psychosocial impact **Certainty of evidence:** Not applicable	*This outcome is important to patients because gender incongruence is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning.* **No evidence was identified for this outcome.**
Fertility **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can reduce fertility. Prior to commencing masculinising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* **No evidence was identified for this outcome.**

Outcome	Evidence statement
Feasibility of masculinising genital surgery **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can have an impact on surgical outcomes. Treatment may alter the amount of genital tissue available for phalloplasty, metoidioplasty, hysterectomy and bilateral salpingo-oophorectomy.* **No evidence was identified for this outcome.**
Cognitive outcomes **Certainty of evidence:** Not applicable	*This outcome is important to patients because masculinising medicines can negatively impact cognitive processes such as concentration, memory, and executive function.* **No evidence was identified for this outcome.**
Detransition after receipt of masculinising 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 masculinising medicines **Certainty of evidence:** Not applicable	*This outcome is important to patients because some patients who choose to take masculinising medicines may regret this decision. Regret may or may not be associated with detransition.* **No evidence was identified for this outcome.**
Safety	
Safety **Certainty of evidence:** 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 CYP: children and young people; GnRH: gonadotrophin-releasing hormone	

In CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation, what is the cost-effectiveness of testosterone with GnRH analogues with or without psychological and psychosocial support compared to one or a combination of psychological support or social transitioning to the desired gender or with no intervention?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified for cost-effectiveness.**
Abbreviations CYP: children and young people; GnRH: gonadotrophin-releasing hormone	

From the evidence selected, are there any subgroups of patients that may benefit from treatment with testosterone with GnRH analogues with or without psychological and psychosocial support more than the wider population of interest?

Subgroup	Evidence statement
	No evidence was identified regarding any subgroups of patients that may benefit from treatment with testosterone with GnRH analogues with or without psychological and psychosocial support more than the wider population of interest.
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 testosterone for those aged 16 up to their 18th birthday?**
c) **What were the starting criteria, formulation, duration and dose of GnRH analogue treatment for those aged 16 years up to their 18th birthday?**
d) **Did any CYP aged 15 years or younger receive testosterone with GnRH analogues for gender transition? If so, in what circumstances?**
e) **What monitoring was in place for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation receiving testosterone with GnRH analogues?**

f) What were the exclusion criteria in the studies?

Outcome	Evidence statement
Definitions of gender incongruence	**No evidence was identified to address the sub-questions.**
Testosterone dosing	
GnRH analogue dosing	
Testosterone and GnRH analogue for those <15 years	
Monitoring arrangements	
Study exclusion criteria	
Abbreviations CYP: children and young people; GnRH: gonadotrophin-releasing hormone	

6. Discussion

No evidence on the clinical effectiveness, safety or cost-effectiveness of masculinising medicines comprising testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation was identified.

Searches were conducted on four databases for studies published between January 2005 and 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-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 masculinising medicines comprising testosterone with GnRH analogues with or without psychological and psychosocial support compared with one or a combination of psychological support or social transitioning to the desired gender or with no intervention for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation. Published comparator about the effectiveness of testosterone with GnRH analogues 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 masculinisation, what is the clinical effectiveness of treatment with testosterone with GnRH analogues 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 masculinisation, what is the short-term and long-term safety of testosterone with GnRH analogues 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 masculinisation, what is the cost-effectiveness of testosterone with GnRH analogues 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 masculinisation that may benefit more from treatment with testosterone with GnRH analogues 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 testosterone for those aged 16 up to their 18th birthday?
    c) What were the starting criteria, formulation, duration and dose of GnRH analogue treatment for those aged 16 years up to their 18th birthday?
    d) Did any CYP aged 15 years or younger receive testosterone with GnRH analogues for gender transition? If so, in what circumstances?
    e) What monitoring was in place for CYP with gender incongruence who identify as non-binary and wish partial physical masculinisation receiving testosterone with GnRH analogues?
    f) 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 masculinisation. [Some terms used to describe this population include, but are not limited to, agender, gender fluid, non-binary transmasculine, transmasc, genderqueer, gender diverse, polygender, 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 testosterone with GnRH analogues • 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	Masculinising medicines comprising testosterone with GnRH analogues. Individuals taking masculinising medicines may also be receiving psychological or psychosocial support. [Masculinising 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. Testosterone can be given an as intramuscular injection (IM), oral tablet or applied as a gel. Examples include: testosterone gel (Tostran, Testogel, Testim, Testavan), short-acting intramuscular injections such as testosterone propionate, phenypropionate, isocaproate and decanoate (Sustanon), testosterone enantate (Delatestryl) and long-acting injection testosterone undecanoate (Nebido, Roxadin, Aveed), oral testosterone capsules in the form of testosterone undecanoate (Restandol Testocaps, Andriol testocaps, Jatenzo, Kyzatrex, Tlando). GnRH analogues may be referred to as LHRH analogues or LHRH agonists. 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 masculinising medicines. This PICO excludes individuals taking testosterone 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 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>* • **Masculinising 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.* [Masculinising physical changes can include: menstrual cycling, facial/body/head hair, body shape, voice changes, sexual and genital effects. 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 masculinising medicines can reduce fertility. Prior to commencing masculinising medicines patients should be counselled on the impact of treatment on their fertility and offered fertility preservation options.* [Examples of fertility outcomes include, but are not limited to ovulation, pregnancy as well as pregnancy outcomes.] • **Feasibility of masculinising genital surgery** *This outcome is important to patients because masculinising medicines can have an impact on surgical outcomes. Treatment may alter the amount of genital tissue available for phalloplasty, metoidioplasty, hysterectomy and bilateral salpingo-oophorectomy.* • **Cognitive outcomes**

	This outcome is important to patients because masculinising 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 masculinising 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 masculinising medicines** *This outcome is important to patients because some patients who choose to take masculinising 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 events, pancytopenia, polycythaemia, reduced bone density, pre-diabetes (glycosylated haemoglobin (HbA1c) 42mmol/mol – 47mmol/mol, 6% vs 6.4%) or diabetes (HbA1c ≥48mmol/mol, ≥6.5%), QT prolongation on ECG, hypertension, pulmonary oil microembolism. o Anaemia, breast, ovarian or endometrial cancer, , migraine or seizures, sleep apnoea, sexually transmitted infections, hot flushes, night sweats, headaches, migraines, vision disorder, muscle pain, reduced libido, sleep apnoea, jaundice, impaired liver function, nausea, vomiting, haemorrhage (bleeding), inflammation of lungs or lung disease, gynaecomastia, skin reactions, severe acne and for those with diabetes, worsening control e.g. increase in HbA1c despite treatment or as defined in study.

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

Appendix B Search strategy

Medline, Embase, PsycINFO and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Searches were not limited by hormone type (masculinising / feminising); this was to ensure that the widest selection of papers were included in the search. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, guidelines, case reports and resource utilisation studies were excluded.

Search dates: 01 January 2005 and 13 June 2025

Gender affirming hormone therapy search:

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

GNRH search:

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 (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.

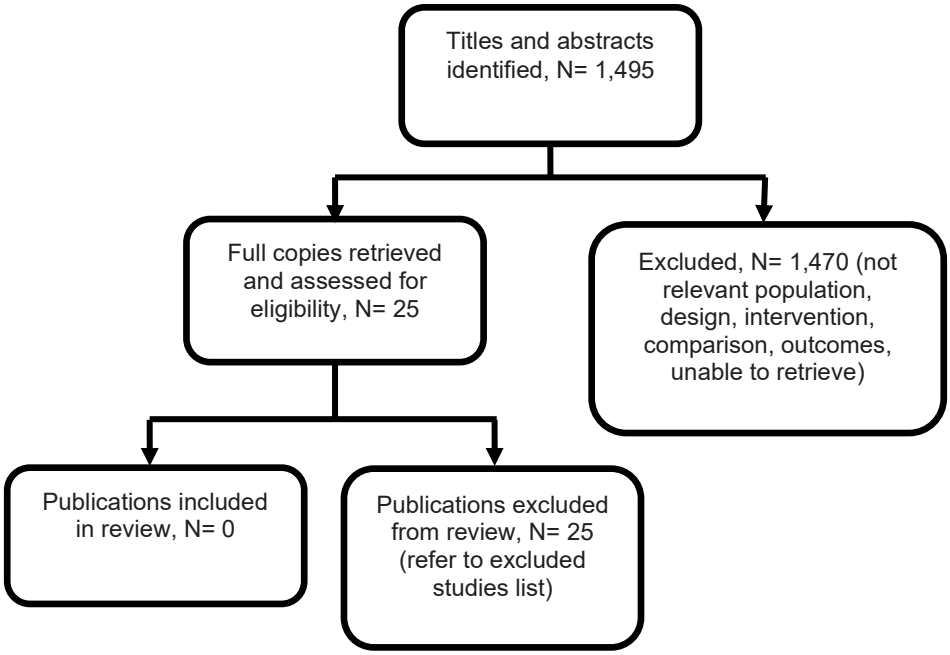
29 25 and 28

30 27 or 29

Appendix C Evidence selection

The literature searches identified 1,495 references. These were screened using their titles and abstracts and 25 references were obtained in full text and assessed for relevance. Of these, 0 references are included in the evidence summary. The remaining 25 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
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.	Retrospective case series (n=143) of a mixed population (children and adolescents attending a gender clinic in the Netherlands who were started on GnRH analogue monotherapy). 125 (89 transboys) followed with subsequent GAHT. Intervention out of scope - GnRH analogue monotherapy followed by GAHT if given. No mention of including non-binary people.
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.	Discharge outcome analysis (n=1,089) of a mixed population (transgender young people referred to paediatric endocrine clinics). No mention of including people on testosterone with GnRH analogues in the study.
Cheung AS. Adult Height in Transgender Youth Who Receive GnRH Analogues Followed by Gender-Affirming Hormone Therapy. J Clin Endocrinol Metab. 2025;110(2):e538-e9.	Publication out of scope – commentary.
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.	Narrative SR of mixed population (transgender adolescents on GnRH analogues, GAHT, antiandrogens, and/or progestins). Results not reported separately for in scope population.
Feigerlova E. Prevalence of detransition in persons seeking gender-affirming hormonal treatments: a systematic review. J Sex Med. 2025;22(2):356-68.	Narrative SR of a mixed population (transgender persons on GnRH analogues and/or GAHT). Results not reported separately for in scope population.
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.	Population out of scope - non-binary people excluded.
Kain EJ, Fuqua JS, Eugster EA. A Retrospective Study of the Use of Gonadotropin-Releasing Hormone Analogs and Testosterone in Transgender Boys: Who, What, When, and for How Long? Transgend Health. 2024;9(4):357-60.	Retrospective case series (n=101) of transgender boys. 44% of total sample were on GnRH analogues and 70% of total sample were on testosterone. % on testosterone with GnRH analogues not reported and results not reported separately for this group.
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.	SRMA of effectiveness of GAHT on cognitive function in mixed population (transgender young adults). None of the studies included GnRH analogues with testosterone. Authors noted that non-binary individuals were absent from published literature.
Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.	Retrospective case series (n=84) of a mixed population (youth with a diagnosis of gender dysphoria at a centre in Canada). Intervention out of scope - GnRH analogues given for puberty suppression. No mention of including non-binary people.
Klaver M, de Mutsert R, Wiepjes CM, Twisk JWR, den Heijer M, Rotteveel J, et al. Early Hormonal Treatment Affects Body Composition and Body	Retrospective case series (n=71 TW and 121 TM) of a mixed population (adolescents diagnosed with gender dysphoria at a centre in the Netherlands). Intervention out of scope - GnRH analogue monotherapy given for puberty suppression followed

Study reference	Reason for exclusion
Shape in Young Transgender Adolescents. J Sex Med. 2018;15(2):251-60.	by GAHT from 16 years of age. No mention of non-binary people.
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.	Retrospective case series (n=38) of a mixed population (young people from ages 12 to 15 years, at Tanner stage 2+ and accessing GnRH analogues followed by GAHT at an endocrine centre). Intervention out of scope - GnRH analogue monotherapy followed by subsequent GAHT.
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.	Retrospective cohort study (n=668) of a mixed population (transgender adolescents referred for endocrine intervention). 279 AFAB consented to GnRH analogues and 136 consented to GAHT after GnRH analogues (results not reported separately for this group). No mention of AFAB taking GnRH analogues with testosterone. No mention of including non-binary people.
Nokoff NJ, Bothwell S, Rice JD, Cree MG, Kelsey MM, Moreau KL, et al. Insulin sensitivity, body composition and bone mineral density after testosterone treatment in transgender youth with and without prior GnRH agonist therapy. J Clin Transl Endocrinol. 2024;36:100356.	Longitudinal observational study (n=19) of adolescent transgender participants AFAB on testosterone. Only includes one patient in-scope (non-binary on testosterone with GnRH analogues).
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.	Intervention out of scope - none of the participants were receiving testosterone.
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.	Cohort study (n=219) of a mixed population (TG adolescents). Subgroup of 62 patients were given GnRH analogues with testosterone. Results not reported separately for in-scope intervention. No mention of including non-binary people.
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.	Case control study (n=3,414) of a mixed population (transgender youth). 13.4% of total sample prescribed GnRH analogues and 20.6% of total sample prescribed testosterone. No mention of including non-binary people. Results not reported separately for in scope population.
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.	Cross sectional study (n=56) of a mixed population (transgender youth on GAHT). 21 AFAB were on testosterone, of whom 5 had prior GnRH analogues (not with testosterone). Intervention out of scope - GnRH analogue monotherapy followed by subsequent GAHT. No mention of including non-binary people.
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.	Observational prospective study (n= 51 transgirls and 70 transboys receiving GnRH analogues and 36 transgirls and 42 transboys receiving GnRH analogues and GAHT). Intervention out of scope - GnRH analogue treatment given for puberty suppression. No mention of non-binary people.
Schulmeister C, Millington K, Kaufman M, Finlayson C, Kennedy JO, Garofalo R, et al. Growth in Transgender/Gender-Diverse Youth in the First Year	Prospective observational study (n=55) of a mixed population (TGD youth initiating GnRH analogue treatment for puberty suppression). Intervention out

Study reference	Reason for exclusion
of Treatment With Gonadotropin-Releasing Hormone Agonists. J Adolesc Health. 2022;70(1):108-13.	of scope – GnRH analogue treatment for puberty suppression.
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.	Retrospective case series (n=106) of a mixed population (children and adolescents with gender dysphoria referred to a gender dysphoria clinic in Israel). Results not reported separately for in scope intervention. No mention of including non-binary people.
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.	Retrospective case series (n=310) of a mixed population (CYP with gender incongruence seeking gender affirming medical care). GnRH analogues was commenced contemporaneously with sex steroid therapy in 91 patients but number that were on testosterone with GnRH analogues not reported. Results not reported separately for in scope population.
Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. J Sex Med. 2019;16(9):1459-68.	Retrospective case series (n=62) of a mixed population (adolescents with gender dysphoria who had received testosterone for a minimum of 6 months). Population out of scope - GnRH analogue treatment for puberty suppression. No mention of including non-binary people.
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.	Case control study (n=4,172 cases) of a mixed population (transgender and gender-diverse youth). Results not reported separately for non-binary people on testosterone with GnRH analogues.
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.	Retrospective cohort study (n=1,766) of a mixed population (children and adolescents who were referred for evaluation of gender dysphoria and/or treated following the Dutch Protocol). Population out of scope - GnRH analogue treatment for puberty suppression. No mention of including non-binary people.
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.	Retrospective study (n=322) of mixed population (people who visited a gender clinic in Amsterdam). Intervention out of scope – GnRH analogue monotherapy followed by subsequent testosterone. No mention of including non-binary people.

Abbreviations

AFAB: assigned female at birth; CYP: children and young people; GAHT: gender-affirming hormone therapy; GnRH: gonadotropin-releasing hormone; SR: systematic review; SRMA: systematic review and meta-analysis; TG: transgender; TGD: transgender and gender-diverse; TM: trans men; TW: trans women

Appendix E Evidence table

No studies assessing the clinical effectiveness, safety or cost-effectiveness of testosterone with GnRH analogues for children and young people with gender incongruence who identify as non-binary and wish partial physical masculinisation 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 testosterone with GnRH analogues for children and young people with gender incongruence who identify as non-binary and wish partial physical masculinisation 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 or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Child and/or young person	In law, everyone under 18 years of age is a child (Children Act 1989) but we recognise that it may be more appropriate to refer to those approaching the age of 18 as a young person, and that such young people may not recognise themselves as a "child". In places, we have referred only to "young person", or only to "child", for example where treatment in question is only given towards the later stages of childhood, closer to the age of 18, or in reference to the parent/ child relationship, in which they remain the parents' child, regardless of their age. Otherwise, we have used the phrase "child and/or young person" throughout the report for this reason only, and do not intend there to be a material difference between them other than that.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
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).
Cost effectiveness analysis	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
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. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5) is the latest version.
Dutch Approach	Protocol published in 1998 by the Amsterdam child and adolescent gender identity clinic. The protocol set out that young people being considered for treatment for gender dysphoria with the use of puberty blockers must meet the following criteria: • minimum age 12; • life-long gender dysphoria increased around puberty; • psychologically stable without serious comorbid psychiatric disorders that might interfere with the diagnostic process; and • have family support.

[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]
Feminising and masculinising hormones (also known as cross-sex hormones, and gender affirming hormones)	Sex hormones given as part of a medical transition for gender dysphoric individuals (testosterone for transgender males and oestrogen for transgender females).
Gender dysphoria	Diagnostic term used by health professionals and found in DSM-5 outlined above. Gender dysphoria describes “a marked incongruence between one’s experienced/ expressed gender and assigned gender of at least six months duration” which must be manifested by a number of criterion.
Gender 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. 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) (GnRHa)	Taking these hormones stops the progress of puberty. The GnRH analogues (puberty blockers) act by competing with the body’s natural gonadotrophin releasing hormone. This competition blocks the release of two gonadotrophin hormones important in puberty called Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
International Classification of Diseases 11th Revision (ICD-11)	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. It is developed and annually updated by the World Health Organization (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.
Paediatrics	The branch of medicine dealing with children and their medical conditions.
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).

Term	Definition[1]
Psychosocial	Describes the psychological and social factors that encompass broader wellbeing.
Puberty blockers	See gonadotropin-releasing hormone analogues above.
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
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