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PATHWAYS TRIAL, PATHWAYS HORIZON INTENSIVE, PATHWAYS CONNECT

Submission date
04/12/2025

Recruitment status
Recruiting

Registration date
17/12/2025

Overall study status
Ongoing

Last Edited
17/07/2026

Condition category
Other

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The PATHWAYS Trial is a clinical study investigating the effects of puberty-suppressing medication in children and young people (CYP) who experience gender incongruence. Gender incongruence is when a person's gender identity does not match the sex they were registered as at birth. This can cause significant emotional distress, particularly during puberty, when the body begins to develop secondary sex characteristics.
The medication being studied is a gonadotropin-releasing hormone analogue (GnRHa), which temporarily pauses puberty. Although this treatment is already used in some countries, there is limited high-quality evidence about its benefits and risks in this context.
The PATHWAYS Trial aims to provide robust, independent evidence possible on benefits and harms.

Who can participate?
To take part in PATHWAYS TRIAL, a young person must be attending the NHS Gender Service and have a clinical diagnosis of gender incongruence. The young person will have a series of tests and scans to check whether they can take part in the trial. These include bone scans, blood and urine tests, and something called a Tanner stage assessment, which is when a doctor looks at their body to know which stage of puberty they are at. The young person must be in puberty – between early and later puberty. This is checked on examination by a doctor. The young person must also be younger than 15 years and 11 months to take part in PATHWAYS TRIAL. To join the trial, young people cannot have previously taken puberty-suppressing hormones or cross-sex hormones.

What does the study involve?
Participants will be randomly assigned to an offer to start treatment either immediately or after a 1-year delay. The two groups will be compared over 2 years to assess how the timing of treatment affects quality of life, mental health, physical development, cognitive function, and gender related distress. Young people will be followed up for the funding period, up to another 2.5 years. There will then be longer-term follow-up, both through data linkage and active follow-up through further funding.
Participants will attend regular clinic visits, complete questionnaires, and undergo health checks, including blood tests and scans.

Another related study, PATHWAYS HORIZON-Intensive, will follow a comparison group of 300 young people who are not receiving GnRHa, to help understand the broader effects of different care pathways. Some participants (150 from Trial, 100 from HORIZON-Intensive) will also take part in brain imaging and cognitive assessments through a linked study called PATHWAYS CONNECT.

What are the possible benefits and risks of participating?
We do not know whether the treatment may help participants. By taking part in this study, participants may help us learn more about what children and young people with gender incongruence find good or not so good about puberty-suppressing hormone (GnRHa) treatment. This information might help young people, parents and doctors in the future make decisions about this treatment.
These medicines are already used for other conditions, like early puberty, and most side effects are mild and go away when treatment stops. Common short-term effects include headaches, hot flushes, tiredness, mood changes, and soreness where the injection is given. Some people may feel more anxious or low in mood, so we will check in with participants regularly about how they are feeling.
There are also some less common but important risks. These medicines can affect the bones by slowing down bone strength development. We will monitor growth and bone health during the study. Rarely, a condition called idiopathic intracranial hypertension (IIH) can happen, which causes severe headaches, vision problems, or ringing in the ears.
There is also a very small chance of changes in heart rhythm, especially if participants take certain other medicines, so we will check participants health history and may do an ECG (heart tracing) if needed.
Some risks may not show up until later in life. These include possible effects on:
1. Fertility (the ability to have children in the future if participants go on to have cross sex hormones like testosterone or oestrogen)
2. Bone health (risk of weaker bones or fractures later)
3. Sexual development and function
4. Memory and thinking skills (we do not yet know if there is an effect and presently the risk is theoretical)
To examine bone density (strength) the trial involves DEXA scans of the spine and hips and x-rays of the left hand/wrist. Some of these will be extra to those that someone would have if they did not take part. These procedures use ionising radiation to form images of the body and provide doctors with other clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous.
We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will add only a very small chance of this happening to participants.
Taking a blood sample is usually safe but there are a few things that could happen:
1. Feeling a little pain when the needle goes in (like a small pinch)
2. Bruising or a small bump where the needle was
3. Bleeding, but usually this is small and stops quickly
4. Feeling dizzy or faint, especially if nervous about needles or blood
5. Infection, but this is very rare and hospital staff keep things clean to prevent this from happening

Where is the study run from?
Recruitment will take place through NHS Gender Services for Children and Young People across England. It is sponsored by King's College London and South London and Maudsley NHS Foundation Trust (UK).

When is the study starting and how long is it expected to run for?
The study is expected to start in early 2026 and expected to run until June 2030.

Who is funding the study?
The research is funded by the National Research Collaboration Programme (NRCP), an NHS England and National Institute for Health and Care Research (NIHR) partnership (UK).

Who is the main contact?
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Contact information

Type(s)
Principal investigator, Scientific, Public

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Additional identifiers

Integrated Research Application System (IRAS)
1011645

Central Portfolio Management System (CPMS)
66902

National Institute for Health and Care Research (NIHR)
167530

Study information

Scientific Title
Puberty Suppression and Transitional Healthcare with Adaptive Youth Services (PATHWAYS): PATHWAYS TRIAL, PATHWAYS CONNECT and PATHWAYS HORIZON-INTENSIVE

Acronym
PATHWAYS

Study objectives

Primary Objective:
To determine the short/medium-term benefits and risks of GnRHa for puberty suppression in CYP with gender incongruence. This will take a comprehensive approach to domains of possible benefit and risk, including quality of life, mental health, gender identity/dysphoria and body satisfaction, impact on cognition and brain development and physical effects including bone mineral density. For the purposes of this study, short-term refers to effects during the early stages of intervention, e.g., typically in the first 3 to 6 months while medium-term refers to effects at the trial endpoint.

Secondary objectives:
1. To understand which potential outcomes e.g., (domains of quality of life, mental health, gender and body distress, cognition, physical health) are the priority goals for CYP receiving GnRHa.
2. To describe the characteristics of those seeking GnRHa:
2.1. Evaluate psychosocial functioning
2.2. Assess mental health outcomes
2.3. Examine gender dysphoria and body image
2.4. Monitor physical health and development
2.5. Understand cognitive and brain development
2.6. Explore safety and adverse events
2.7. Investigate fertility preservation decisions
2.8. Understand the role of neurodevelopmental and mental health diagnoses
2.9. Assess the impact of social and environmental factors
3. To describe what decisions CYP make at the end of GnRHa in terms of gender care, including remaining on GnRHa, moving to cross-sex hormones, or stopping/pausing endocrine interventions.
4. To link trajectories of brain development to cognitive measures, including general intelligence, memory and executive function.
5. To engage CYP and their parents participating in TRIAL and HORIZON INTENSIVE in the study methods and findings in order to promote longer-term follow-up that will provide an opportunity to understand their choices around gender identity and gender care, as well as their outcomes in the above domains as they enter adult life.

Exploratory objectives:
1. Do short-term/risk benefit profiles vary according to chronological age and/or Tanner stage?
2. Do risk benefit profiles vary according to birth-registered sex?
3. Do risk benefit profiles vary according to presence or not of neurodevelopmental disorders or high levels of neurodevelopmental traits?
4. Do risk benefit profiles vary according to length of GnRHa treatment?

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/11/2025, London City and East Research Ethics Committee (2nd Floor 2 Redman Place Stratford, London, E20 1JQ, United Kingdom; N/A; cityandeast.rec@hra.nhs.uk), ref: 25/LO/0500

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Open (masking not used)

Control
Active

Assignment
PATHWAYS TRIAL: Immediate vs Delayed (12 months) GnRHa Treatment. 226 participants total. PATHWAYS HORIZON INTENSIVE: Non-randomised, intensive observational control cohort broadly matched to PATHWAYS TRIAL participants. 300 participants total. PATHWAYS CONNECT: 150 participants from TRIAL, 100 participants from HORIZON INTENSIVE. 250 participants total.

Purpose
Treatment

Study type(s)

Health condition(s) or problem(s) studied
Gender incongruence

Interventions
The PATHWAYS TRIAL is designed as a Randomised Controlled Trial (RCT) comparing immediate vs. delayed start (at 1 year post-randomisation) of GnRHa amongst 226 CYP with primary endpoint at 2 years post-randomisation. Participants will be randomised 1:1 to immediate or delayed treatment with Gonadotropin Releasing Hormone Agonists (GnRHa). Midpoint comparisons determine short-term differences due to receipt of GnRHa while endpoint comparisons determine whether the groups converge or GnRHa timing/duration influences outcome. All participating CYP and their parents/legal guardians will be asked to assent/consent to longer-term follow-up, which in the first instance will be for the life of the funding (total period 5.5 years).

HORIZON INTENSIVE is a non-randomised comparison group of CYP (n = 300) not receiving GnRHa who are broadly matched on key participant characteristics: clinical centre, birth-registered sex, presence of a neurodevelopmental disorder or high level of traits and chronological age. They will complete the same physical, physiological and cognitive measures as TRIAL participants, although only at baseline and endpoint. As CYP who experience gender incongruence may differ from the general population of same-aged CYP, these data will provide a comprehensive comparison to aid interpretation of the effects of GnRHa.

PATHWAYS CONNECT is a magnetic resonance (MR) brain imaging study to examine whether the use of GnRHa alters the trajectories of brain development. PATHWAYS CONNECT will recruit a subset of CYP enrolled in TRIAL (n = 150) and HORIZON INTENSIVE (n = 100) to participate in serial brain imaging over the same 2-year time course.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Triptorelin, leuprorelin acetate

Primary outcome(s)
1. Quality of life measured using KIDSCREEN-10 Electronic Participant Reported Outcome (ePRO) at Baseline, month 6, month 12, month 18, month 24, and annually during follow up period (months 36 and 48) for TRIAL participants; For HORIZON INTENSIVE participants: Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

Key secondary outcome(s)
1. Quality of life measured using KIDSCREEN-52 ePRO at Baseline, month 6, month 12, month 18, month 24, and annually during follow up period (months 36 and 48) for TRIAL participants; For HORIZON INTENSIVE participants: Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

2. Gender-related distress measured using Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

3. Mental health symptoms measured using Revised Children's Anxiety and Depression Scale (RCADS) ePRO at Baseline, month 3, month 6, month 12, month 15, month 18, month 24, and annually during follow up period (months 36 and 48) for TRIAL participants. For HORIZON INTENSIVE participants: Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

4. Gender-related distress measured using Body Image Scale – Gender Spectrum (BIS-GS) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

5. Gender-related distress measured using Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

6. Mental health symptoms measured using SCOFF questionnaire ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

7. Gender identity measured using Sexual attraction questionnaire (participants 12+) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

8. Gender identity measured using ALSPAC Romantic Relations measure (participants 12+) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

9. Gender identity measured using Gender Identity Question ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

10. Mental health symptoms measured using Adolescent Primary Care Traumatic Stress Screen (APCTSS) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

11. Physical health diagnoses measured using participant reported/clinician assessed at ongoing

12. Rates of suicidal ideation measured using Ask Suicide-screening Questions (ASQ) ePRO at Baseline, month 3, month 6, month 12, month 15, month 18, month 24, and annually during follow up period (months 36 and 48) for TRIAL participants. For HORIZON INTENSIVE participants: Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

13. Behavioural and functional difficulties measured using Child Behaviour Checklist (CBCL) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

14. Behavioural and functional difficulties measured using Youth Self-Report (YSR) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

15. Mood symptoms measured using Difficulties in Emotion Regulation Scale – 18 (DERS-18) ePRO at Baseline, month 12, month 24, annually during follow up period (months 36 and 48)

16. Hospitalisations of participants measured using participant reported/clinician assessed at ongoing

17. Rates of referral to, uptake of, and completion of psychological therapy, occupational therapy, speech and language therapy, clinical nursing, youth work support, school/college support, and non-endocrine pharmacological treatments measured using participant reported /clinician assessed at ongoing

18. Cognitive function (intellectual functioning) measured using Wechsler Intelligence Scale for Children (WISC-V) researcher/psychologist administered at Baseline, month 12, month 24 for TRIAL participants; For HORIZON INTENSIVE participants: Baseline and month 24

19. Cognitive Function (executive function) measured using Delis-Kaplan Executive Function System (D-KEFS) researcher/psychologist administered at Baseline, month 12, month 24 for TRIAL participants; For HORIZON INTENSIVE participants: Baseline and month 24

20. Cognitive function (learning and memory) measured using Child and Adolescent Memory Profile (CHAMP) researcher/psychologist administered at Baseline, month 12, month 24 for TRIAL participants; For HORIZON INTENSIVE participants: Baseline and month 24

21. Cognitive Function (memory) measured using Memory Validity Profile (MVP) researcher /psychologist administered at Baseline, month 12, month 24 for TRIAL participants; For HORIZON INTENSIVE participants: Baseline and month 24

22. Cognitive function (executive function) measured using Behaviour Rating Inventory of Executive Function (BRIEF2) researcher/psychologist administered at Baseline, month 12, month 24 for TRIAL participants; For HORIZON INTENSIVE participants: Baseline and month 24

23. Body Mass Index (BMI) measured using physiological measurement at Baseline, month 6, month 12, month 18, month 24 for TRIAL participants. For HORIZON INTENSIVE participants: Baseline, month 24

24. Bone mineral density measured using DEXA scan at Baseline, month 12, month 24, and annually during follow up period (months 36 and 48) for TRIAL participants. For HORIZON INTENSIVE participants: Baseline and month 24

25. Blood pressure measured using physiological measurement at Baseline, month 6, month 12, month 18, and month 24 for TRIAL participants. For HORIZON INTENSIVE participants: Baseline, month 24

26. Sex hormone and bone health related markers measured using blood tests at Baseline, month 6, month 12, month 18, and month 24 for TRIAL participants. For HORIZON INTENSIVE participants: Baseline, month 24

27. Adverse events measured using participant reported/clinician assessed at ongoing

28. Puberty staging assessment - Tanner staging measured using physical assessment at Baseline, month 12 (optional), and month 24 (optional) for TRIAL participants only

29. Puberty staging assessment – self-reported measured using participant-reported outcome at Baseline, month 12, month 24 for TRIAL participants; For HORIZON INTENSIVE participants: Baseline and month 24

30. Brain structure: longitudinal trajectories of brain tissue volume measured using MRI - standard weighted T1 and T2 images at Baseline, month 12, month 24 for participants consenting to PATHWAYS CONNECT; For HORIZON INTENSIVE participants: Baseline and month 24

31. Brain structure: longitudinal trajectories of microstructure in cortical white matter measured using Diffusion MRI and T2* images at Baseline, month 12, month 24 for participants consenting to PATHWAYS CONNECT; For HORIZON INTENSIVE participants: Baseline and month 24

32. Brain metabolites: longitudinal changes in brain metabolites in the globus pallidus and putamen (basal ganglia) measured using Magnetic Resonance Spectroscopy at Baseline, month 12, month 24 for participants consenting to PATHWAYS CONNECT; For HORIZON INTENSIVE participants: Baseline and month 24

33. Brain function: Functional connectivity between the basal ganglia (and other sub-cortical structures) with cortex measured using Functional MRI at Baseline, month 12, month 24 for participants consenting to PATHWAYS CONNECT; For HORIZON INTENSIVE participants: Baseline and month 24

Completion date
31/01/2031

Eligibility

Key inclusion criteria
Current inclusion criteria as of 17/07/2026:
TRIAL Clinical Inclusion Criteria:
1. The child or young person meets diagnostic criteria for gender incongruence according to ICD-11. This diagnosis should be made or confirmed within the CYPGS. Specifically:
1.1. The CYP has a strong desire to be a different gender than the birth-registered sex
1.2. The CYP has a strong dislike of sexual anatomy or anticipated secondary sex characteristics
1.3. The incongruence must have persisted for a minimum of 2 years
1.4. The CYP has a strong desire to ‘transition’, to live and be accepted as a person of the experienced gender

2. The CYP wants puberty suppression for their gender incongruence and this care preference persists after receiving other care deemed appropriate from the CYPGS and other sources prior to the initiation of GnRHa
3. The CYP is confirmed by the CYPGS to be in Tanner stage 2-5
4. Age: At the time of randomisation, for birth-registered females, the CYP is between 11 years and up to the 16th birthday; For birth-registered males, the CYP is between 12 years and up to the 16th birthday
5. The clinician in the CYPGS leading on care for that CYP considers that GnRHa for puberty suppression offers a reasonable prospect of benefit. This benefit might be achieved in relation to quality-of-life parameters (e.g., confidence in peer and family relations, participation in school and/or leisure activities, improved sense of well-being), mental or physical health.
6. The clinician in the CYPGS leading on care for an individual patient considers they have participated sufficiently for their holistic health and well-being in other forms of care for puberty suppression to be considered, in line with NMDT recommendations and this participation is reviewed by the NMDT.
7. The CYP has demonstrated sufficient understanding of the possible advantages and disadvantages of the proposed treatment including immediate psychological and physical impacts and also long-term implications, benefits and harms in the context of their personal situation and needs. Having considered this information, the child or young person has indicated that they wish to proceed with the treatment (assented).
7.1. To achieve this, this will involve serial discussions with clinicians, including those with specialist knowledge of endocrine interventions (e.g., paediatric endocrinologist, clinical nurse specialist, paediatrician with specialistic knowledge)
7.1.1. There will be written information provided and recording of how the child or young person flexibly demonstrates an understanding of possible risks and benefits
7.1.2. Information may also be provided in other, additional formats that are bespoke for the individual child or young person's cognitive and learning style. For example, this may include visual supports and audio recordings
7.1.3. The child or young person will be asked to explain their understanding of treatment with GnRHa in their own words
7.1.4. A checklist will be used by the clinical services to ensure all key points have been covered and understood
7.2. Fertility preservation will have been discussed with each CYP, with developmentally appropriate and/or adapted language/ other forms of communication (as described above) descriptions of what would be involved, how it can be accessed, and the potential long-term implications if fertility preservation is not accessed. CYP will not be referred to the Trial until the NMDT is satisfied this has been adequately considered
8. At least one parent or legal guardian:
8.1. Demonstrated sufficient understanding of the nature and purpose of the proposed treatment, including the possible advantages and disadvantages of the treatment such as immediate psychological impacts and long-term implications, specifically including fertility preservation options, in the context of their CYP's personal situation and needs. This should also include the fact that there may be risks or benefits that are currently unknown
8.2. Demonstrated that they can retain the key parts of that relevant information for a sufficient period to enable them to use and weigh that relevant information to give their informed consent to the proposed intervention
9. The CYP and parent(s)/legal guardian(s) are willing to be randomised into either study arm, documented by signed informed consent (parent/guardian) and assent (CYP)

TRIAL Research Inclusion Criteria:
1. The clinician in the CYPGS believes that GnRHa for a period of 2 or more years may be helpful to the CYP. Particularly, there is no current plan to initiate cross-sex hormone treatment during

the trial period
2. Written informed assent and consent from CYP and parent/legal guardian respectively
3. The CYP and their parent have reviewed the suite of measures, including physical health investigations, cognitive assessments and questionnaires, and understand that their completion is required for the clinical trial
4. Participants who are sexually active agree to use contraception throughout the trial

HORIZON INTENSIVE Inclusion Criteria:
1. Participating in the PATHWAYS HORIZON study
2. Has agreed to be contacted for other research studies when assenting to PATHWAYS HORIZON

CONNECT Inclusion Criteria:
1. Participant is a member of PATHWAYS TRIAL or PATHWAYS HORIZON INTENSIVE
2. Participant is willing to participate in brain imaging study, including travelling to London (King' s College London)
3. Participant provides informed assent (for under 16 years) or consent (for 16+ years)
4. Parent/legal guardian provides consent

Previous inclusion criteria:
TRIAL Clinical Inclusion Criteria:
1. The child or young person meets diagnostic criteria for gender incongruence according to ICD-11. This diagnosis should be made or confirmed within the CYPGS. Specifically:
1.1. The CYP has a strong desire to be a different gender than the assigned sex
1.2. The CYP has a strong dislike of sexual anatomy or anticipated secondary sex characteristics
1.3. The incongruence must have persisted for a minimum of 2 years
1.4. The CYP has a strong desire to 'transition', to live and be accepted as a person of the experienced gender
2. The CYP wants puberty suppression for their gender incongruence and this care preference persists after receiving other care deemed appropriate from the CYPGS and other sources prior to the initiation of GnRHa
3. The CYP is confirmed by the CYPGS to be in Tanner stage 2-5
4. The CYP is younger than 15 years and 11 months at the time of consent to the trial
5. The clinician in the CYPGS leading on care for that CYP considers that GnRHa for puberty suppression offers a reasonable prospect of benefit. This benefit might be achieved in relation to quality-of-life parameters (e.g., confidence in peer and family relations, participation in school and/or leisure activities, improved sense of well-being), mental or physical health.
6. The clinician in the CYPGS leading on care for an individual patient considers they have participated sufficiently for their holistic health and well-being in other forms of care for puberty suppression to be considered, in line with NMDT recommendations and this participation is reviewed by the NMDT.
7. The CYP has demonstrated sufficient understanding of the possible advantages and disadvantages of the proposed treatment including immediate psychological and physical impacts and also long-term implications, benefits and harms in the context of their personal situation and needs. Having considered this information, the child or young person has indicated that they wish to proceed with the treatment (assented).
7.1. To achieve this, this will involve serial discussions with clinicians, including those with specialist knowledge of endocrine interventions (e.g., paediatric endocrinologist, clinical nurse specialist, paediatrician with specialistic knowledge)
7.1.1. There will be written information provided and recording of how the child or young person flexibly demonstrates an understanding of possible risks and benefits
7.1.2. Information may also be provided in other, additional formats that are bespoke for the

individual child or young person's cognitive and learning style. For example, this may include visual supports and audio recordings
7.1.3. The child or young person will be asked to explain their understanding of treatment with GnRHa in their own words
7.1.4. A checklist will be used by the clinical services to ensure all key points have been covered and understood
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8.1. Demonstrated sufficient understanding of the nature and purpose of the proposed treatment, including the possible advantages and disadvantages of the treatment such as immediate psychological impacts and long-term implications, specifically including fertility preservation options, in the context of their CYP's personal situation and needs. This should also include the fact that there may be risks or benefits that are currently unknown
8.2. Demonstrated that they can retain the key parts of that relevant information for a sufficient period to enable them to use and weigh that relevant information to give their informed consent to the proposed intervention
9. The CYP and parent(s)/legal guardian(s) are willing to be randomised into either study arm, documented by signed informed consent (parent/guardian) and assent (CYP)

TRIAL Research Inclusion Criteria:
1. The clinician in the CYPGS believes that GnRHa for a period of 2 or more years may be helpful to the CYP. Particularly, there is no current plan to initiate cross-sex hormone treatment during the trial period
2. Written informed assent and consent from CYP and parent/legal guardian respectively
3. The CYP and their parent have reviewed the suite of measures, including physical health investigations, cognitive assessments and questionnaires, and understand that their completion is required for the clinical trial
4. Participants who are sexually active agree to use contraception throughout the trial

HORIZON INTENSIVE Inclusion Criteria:
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2. Has agreed to be contacted for other research studies when assenting to PATHWAYS HORIZON

CONNECT Inclusion Criteria:
1. Participant is a member of PATHWAYS TRIAL or PATHWAYS HORIZON INTENSIVE
2. Participant is willing to participate in brain imaging study, including travelling to London (King's College London)
3. Participant provides informed assent (for under 16 years) or consent (for 16+ years)
4. Parent/legal guardian provides consent

Healthy volunteers allowed
No

Age group
Child

Lower age limit
11 Years

Upper age limit
16 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 17/07/2026:
TRIAL Clinical Exclusion Criteria:
1. Physical conditions where puberty will not commence or advance in a patient. This may include gonadal failure (e.g. due to genetic disorders such as Turner syndrome) or central hypogonadotropic hypogonadism.
2. Unstable physical health. The purpose of this criterion is to ensure that that the CYP is not undergoing concurrent high-intensity physical interventions which might affect their response to GnRHa or their ability to adhere to the trial protocol. These include but are not limited to:
2.1. Very low or very high BMI (or rapid changes in BMI), particularly if there is a concerning trajectory or associated nutritional or metabolic concerns. This could include eating disorders or body dysmorphic disorder.
2.2. Any poorly controlled medical disorder, such as uncontrolled epilepsy, inflammatory bowel disease, cystic fibrosis. This includes any other condition where participation may pose a risk to the individual's health or compromise study integrity.
2.3. Concerns about bone health or significant risk of fractures (this may also include a low baseline bone density).
2.4. QTc interval above 470 milliseconds at screening, or concomitant high-risk QT-prolonging drugs that cannot be ceased
3. Hypersensitivity to gonadotropin releasing hormone (GnRH), its analogues, or to any of its excipients
4. Known congenital long QT syndrome
5. Unstable mental health that may impair ability to provide informed assent/consent or lead to risk of serious harm to self or others. Many CYP with gender incongruence experience anxiety and/or depression which they relate to gender dysphoria or distress. It is not the intention to exclude those with mild to moderate levels of mental health symptoms. However, severe or unstable symptoms may affect the ability to engage in all aspects of the clinical protocol. Examples would include (but are not limited to):
5.1. Severe or profound depression with significant effects on the ability to accurately evaluate choices and future outcomes;
5.2. Severe body dysmorphic disorder that is confounded with secondary sexual characteristics or physique not conforming to the desired gender;
5.3. Active psychotic symptoms;
5.4. Significant risk of harm to self or others as exemplified by consistent suicidal thoughts, repeated and ongoing acts of self-harm and/or the need for emergency plans with the child or young person and family;
6. Aspects of family/home situation that makes it likely the CYP will not be able to adhere to aspects of the protocol such as attending regular follow-up appointments. This last requirement will have been assessed in relation to the CYP's ability to find ways of attending appointments in

the CYPGS.
7. Clinical concerns about the young person's capacity to consent.
8. Insufficient understanding of PATHWAYS TRIAL.
9. New or ongoing safeguarding concerns.
10. Birth-registered females with undiagnosed vaginal bleeding.
11. Birth-registered females who are pregnant or lactating.
12. People of child-bearing potential (i.e. sexually active birth-registered female not using effective contraception as compatible with GnRHa**) who are at risk of pregnancy during the trial.

TRIAL Research Exclusion Criteria:
1. The CYP has previously taken or is currently using GnRHa for this indication. This will be identified by (i) asking CYP and their parents/legal guardians about off-label use and (ii) through hormone blood tests at baseline (all participants). Participants and their parents/legal guardians will be reminded about the safety and legal concerns of off-label use.
2. The CYP is or has taken cross-sex hormones for gender incongruence/dysphoria.
3. The participant is involved in another research trial*
* Specifically, a CTIMP or another intervention that could possibly interfere with involvement in PATHWAYS TRIAL or interpretation of the findings

HORIZON INTENSIVE Exclusion Criteria:
1. Is considered clinically eligible for GnRHa and wishes to receive this intervention
2. A decision regarding clinical eligibility for GnRHa is pending
3. CYP has previously used GnRHa or gender-affirming hormones for gender incongruence

CONNECT Exclusion Criteria:
1. MR imaging is contraindicated (e.g. ferromagnetic metal implants)

Previous exclusion criteria:
TRIAL Clinical Exclusion Criteria:
1. Physical conditions where puberty will not commence or advance in a patient. This may include gonadal failure (e.g. due to genetic disorders such as Turner syndrome) or central hypogonadotropic hypogonadism.
2. Unstable physical health. The purpose of this criterion is to ensure that that the CYP is not undergoing concurrent high-intensity physical interventions which might affect their response to GnRHa or their ability to adhere to the trial protocol. These include but are not limited to:
2.1. Very low or very high BMI (or rapid changes in BMI), particularly if there is a concerning trajectory or associated nutritional or metabolic concerns. This could include eating disorders or body dysmorphic disorder.
2.2. Any poorly controlled medical disorder, such as uncontrolled epilepsy, inflammatory bowel disease, cystic fibrosis. This includes any other condition where participation may pose a risk to the individual's health or compromise study integrity.
2.3. Concerns about bone health or significant risk of fractures (this may also include a low baseline bone density).
2.4. QTc interval above 470 milliseconds at screening, or concomitant high-risk QT-prolonging drugs that cannot be ceased
3. Hypersensitivity to gonadotropin releasing hormone (GnRH), its analogues, or to any of its excipients
4. Known congenital long QT syndrome
5. Unstable mental health that may impair ability to provide informed assent/consent or lead to risk of serious harm to self or others. Many CYP with gender incongruence experience anxiety and/or depression which they relate to gender dysphoria or distress. It is not the intention to

exclude those with mild to moderate levels of mental health symptoms. However, severe or unstable symptoms may affect the ability to engage in all aspects of the clinical protocol. Examples would include (but are not limited to):
5.1. Severe or profound depression with significant effects on the ability to accurately evaluate choices and future outcomes;
5.2. Severe body dysmorphic disorder that is confounded with secondary sexual characteristics or physique not conforming to the desired gender;
5.3. Active psychotic symptoms;
5.4. Significant risk of harm to self or others as exemplified by consistent suicidal thoughts, repeated and ongoing acts of self-harm and/or the need for emergency plans with the child or young person and family;
6. Aspects of family/home situation that makes it likely the CYP will not be able to adhere to aspects of the protocol such as attending regular follow-up appointments. This last requirement will have been assessed in relation to the CYP's ability to find ways of attending appointments in the CYPGS.
7. Clinical concerns about the young person's capacity to consent.
8. Insufficient understanding of PATHWAYS TRIAL.
9. New or ongoing safeguarding concerns.
10. Birth-registered females with undiagnosed vaginal bleeding.
11. Birth-registered females who are pregnant or lactating.
12. Individuals of child-bearing potential (i.e. sexually active birth-registered female not using effective contraception as compatible with GnRHa**) who are at risk of pregnancy during the trial.

TRIAL Research Exclusion Criteria:
1. The CYP has previously taken or is currently using GnRHa for this indication. This will be identified by (i) asking CYP and their parents/legal guardians about off-label use and (ii) through hormone blood tests at baseline (all participants) and for those randomised to delayed start at 12 months. Participants and their parents/legal guardians will be reminded about the safety and legal concerns of off-label use.
2. The CYP is or has taken cross-sex hormones for gender incongruence/dysphoria.
3. The participant is involved in another research trial*
* Specifically, a CTIMP or another intervention that could possibly interfere with involvement in PATHWAYS TRIAL or interpretation of the findings

HORIZON INTENSIVE Exclusion Criteria:
1. Is considered clinically eligible for GnRHa and wishes to receive this intervention
2. A decision regarding clinical eligibility for GnRHa is pending
3. CYP has previously used GnRHa or gender-affirming hormones for gender incongruence

CONNECT Exclusion Criteria:
1. MR imaging is contraindicated (e.g. ferromagnetic metal implants)

Date of first enrolment
05/01/2026

Date of final enrolment
30/06/2028

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre
Bristol Royal Hospital for Children
Upper Maudlin Street
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BS2 8BJ

Study participating centre
Leeds General Infirmary
Great George Street
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LS1 3EX

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Organisation
South London and Maudsley NHS Foundation Trust

ROR
https://ror.org/015803449

Funder(s)

Funder type

Funder Name
National Research Collaboration Programme (NRCP)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.2	20/11/2025	24/02/2026	No	No
Protocol file	version 3.2	18/06/2026	17/07/2026	No	No