
Ethics Question Set

Project Scope

EudraCT ID:

| | |
|--|------------|
| Will any research sites in this study be NHS organisations? | Yes |
| Does the study involve use of any ionising radiation? | Yes |
| Will you be taking new OR existing human tissue samples (or other human biological samples)? | Yes |
| Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves? | No |
| Do you plan to include any participants who are children? | Yes |
| Would you like to apply for Network Support? | Yes |
| Do you plan to include any participants who are prisoners or young offenders? | No |
| Proposed Study End Date | 31/01/2031 |

A. Administrative Details

6. Full title of the research

Details entered here will be entered into Medicines Information A3

Puberty Suppression and Transitional Healthcare with Adaptive Youth Services (PATHWAYS). PATHWAYS TRIAL, PATHWAYS CONNECT, and PATHWAYS HORIZON Intensive.

8. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

Yes No

9. Lay Summary of the study

The PATHWAYS Trial is a UK-wide 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 assigned 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 possible evidence on benefits and harms.

The trial will involve 226 participants under the age of 16 who are eligible for GnRHa. Participants will be randomly assigned to either start treatment immediately or after a one-year delay. The two groups will be compared over two 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.

Participants will attend regular clinic visits, complete questionnaires, and undergo health checks, including blood tests and scans. Some will also take part in brain imaging and cognitive assessments through a linked study called PATHWAYS CONNECT. Another related study, PATHWAYS HORIZON-Intensive, will follow a comparison group of young people who are not receiving GnRHa, to help understand the broader effects of different care pathways.

The research is funded by the National Institute for Health and Care Research (NIHR) and NHS England. It is sponsored by King's College London and South London and Maudsley NHS Foundation Trust. Recruitment will take place through NHS Gender Services for Children and Young People across England.

10. In which aspects of the research process have you actively involved or will you involve patients service users and/or their carers or members of the public?

- Design of the research
- Management of the research
- Undertaking the research
- Analysis of results
- Dissemination of findings
- None of the above

11. Give details of involvement, or if none please justify the absence of involvement.

Public and patient involvement (PPI) has been central to the development and ongoing delivery of the PATHWAYS Trial and its associated studies.

In June 2024, 7 focus groups were held with CYP and their parents/carers, recruited via the NHS England Youth Advisory Forum for the Gender Services.

These sessions focused on the research design and application process, outcome measures for those using puberty suppressing hormones and the best ways to conduct interviews with young people on sensitive topics. CYP highlighted the importance of capturing 'holistic mental health' and raised questions about the potential impact of puberty suppression on learning. Participants confirmed that their priorities were reflected in the KIDSCREEN-52 measure and asked for clear links to be made between medical and physical health outcomes.

Since the study was funded, Advisory Group members have been appointed., called PATHWAYS Engagement This work is led by partner National Children's Bureau, these include young people aged 18+ with a history of/ongoing gender diversity and parents/

carers with an offspring with a history of/ongoing gender diversity. None are/have an offspring attending the CYP Gender Services. Since May 2025, we have had 2 meetings focusing on (1) ensuring gender identity and social transition is adequately described and (2) reviewing Patient Information Sheets for the trial. Based on feedback, gender/social transition questions were extended to capture greater variety of experience. Feedback on the PIS was that the information was clear but more detail about possible benefits and harms was requested (and implemented in this submission).

The Advisory Groups will assist with participant recruitment and retention, co-production of a new measure and qualitative work, data interpretation to ensure findings are meaningful. They will also co-produce plain English progress reports, summaries of results, and advise on dissemination strategies.

12. Is the trial a Complex Innovative Design (CID) trial?

Yes No

B. Research Procedures, Risks and Benefits

1. Non-clinical interventions

(Please complete for each intervention/procedure as follows)

1: Interventions/procedures to be received by each participant as part of the research protocol

2: Number of interventions/procedures which are part of standard care

3: Number of interventions/procedures which are additional to standard care

4: Total number of interventions/procedures

5: Average time taken per intervention/procedure (minutes, hours or days)

6: Details of who will conduct the intervention/procedure and where it will take place

| 1 | 2 | 3 | 4 | 5 | 6 |
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| Informed Assent/Consent | 0 | 1 | 1 | 60 Minutes | Informed consent/assent will take place in the endocrine clinic with the principal/sub-investigator, participant, and their parent/caregiver. |
| [PATHWAYS TRIAL/HORIZON Intensive] Medical History | 1 | 1 | 1 | 15 Minutes | Medical history will be obtained from participants in the endocrine clinic by the principal investigator or sub-investigator. |
| [PATHWAYS TRIAL/HORIZON Intensive] Demographic Data | 1 | 0 | 1 | 5 Minutes | Demographic will be obtained from participants in the endocrine clinic or gender service by a researcher or research nurse. |
| [PATHWAYS TRIAL/HORIZON Intensive] Swanson Nolan and Pelham-IV (SNAP-IV) | 0 | 1 | 1 | 3 Minutes | At baseline visit only, parent/caregiver reported questionnaire will be completed in the endocrine clinic (supported by researcher if required) via electronic patient reported outcomes (ePRO) system online. |

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| [PATHWAYS TRIAL/HORIZON Intensive] Social Communication Questionnaire (SCQ) | 0 | 1 | 1 | 5 Minutes | At baseline visit only, parent/caregiver reported questionnaire will be completed in clinic (supported by researcher if required) via ePRO |
| [PATHWAYS TRIAL] KIDSCREEN-52 | 0 | 3 | 3 | 7 Minutes | TRIAL participants will complete the KIDSCREEN-52 on ePRO during visits to the endocrine clinic at baseline, 12 months, and 24 months. |
| [HORIZON Intensive] KIDSCREEN-52 | 0 | 2 | 2 | 7 Minutes | HORIZON Intensive participants will complete on ePRO at baseline and 24 months. |
| [PATHWAYS TRIAL] Gender Identity Questionnaire | 0 | 3 | 3 | 1 Minute | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months, with clinician support at baseline if required. |
| [HORIZON Intensive] Gender Identity Questionnaire | 0 | 2 | 2 | 1 Minute | HORIZON Intensive participants will complete at baseline and month 24. |
| [PATHWAYS TRIAL] Revised Child Anxiety and Depression Scale (RCADS-25) | 0 | 7 | 7 | 5 Minutes | Trial participants will complete the RCADS-25 on ePRO in the endocrine clinic at baseline and months 6, 12, 18, and 24 with support if requested/required. Additional timepoints at months 3 and 15 will be collected via ePRO remotely. |
| [HORIZON Intensive] Revised Child Anxiety and Depression Scale (RCADS-25) | 0 | 2 | 2 | 5 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Ask Suicide-Screening Questions (ASQ) | 0 | 7 | 7 | 1 Minute | Trial participants will complete the ASQ on ePRO in the endocrine clinic at baseline and months 6, 12, 18, and 24, with support if requested/required. Additional timepoints at months 3 and 15 will be collected via ePRO remotely. |
| [HORIZON Intensive] Ask Suicide-Screening Questions (ASQ) | 0 | 2 | 2 | 1 Minute | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS) | 0 | 3 | 3 | 3 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |

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| [HORIZON Intensive] Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS) | 0 | 2 | 2 | 3 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL/HORIZON Intensive] Body Image Scale – Gender Spectrum (BIS-GS) | 0 | 3 | 3 | 3 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months,. |
| [HORIZON Intensive] Body Image Scale – Gender Spectrum (BIS-GS) | 0 | 2 | 2 | 3 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Difficulties in Emotion Regulation Scale (DERS) | 0 | 3 | 3 | 3 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |
| [HORIZON Intensive] Difficulties in Emotion Regulation Scale (DERS) | 0 | 2 | 2 | 3 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Sexual Attraction Questionnaire | 0 | 3 | 3 | 1 Minute | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |
| [HORIZON Intensive] Sexual Attraction Questionnaire | 0 | 2 | 2 | 1 Minute | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Romantic relations ALSPAC measure | 0 | 3 | 3 | 3 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |
| [HORIZON Intensive] Romantic relations ALSPAC measure | 0 | 2 | 2 | 3 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y) | 0 | 3 | 3 | 3 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |
| [HORIZON Intensive] Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y) | 0 | 2 | 2 | 3 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Adolescent Primary Care Traumatic Stress Scale (APCTSS) | 0 | 3 | 3 | 2 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |

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| [HORIZON Intensive] Adolescent Primary Care Traumatic Stress Scale (APCTSS) | 0 | 2 | 2 | 2 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) | 0 | 3 | 3 | 15 Minutes | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |
| [HORIZON Intensive] Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) | 0 | 2 | 2 | 15 Minutes | HORIZON Intensive participants will complete via ePRO at baseline and month 24. |
| [PATHWAYS TRIAL] SCOFF | 0 | 3 | 3 | 1 Minute | TRIAL participants will complete on ePRO in the endocrine clinic at baseline, 12 months and 24 months. |
| [HORIZON Intensive] SCOFF | 0 | 2 | 2 | 1 Minute | HORIZON Intensive participants will complete via ePRO at baseline and month 24 |
| [PATHWAYS TRIAL - Immediate GnRHa] Telephone check in | 0 | 4 | 4 | 15 Minutes | Participants will be followed up via a telephone call at months 3, 9, 15, and 21 to discuss any adverse events requiring detail and follow up. For immediate GnRHa arm participants, a clinical nurse specialist (CNS) or delegated medical professional will conduct the call at 3 and 15 months. At months 9 and 21, a PATHWAYS researcher will conduct the call. |
| [PATHWAYS TRIAL - Delayed GnRHa] Telephone check in | 0 | 4 | 4 | 15 Minutes | Participants will be followed up via a telephone call at months 3, 9, 15, and 21 to discuss any adverse events requiring detail and follow up. For delayed GnRHa arm participants, a CNS or delegated medical professional will conduct the call at 15 months. At months 3, 9 and 21, a PATHWAYS researcher will conduct the call. |

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| [PATHWAYS TRIAL] General Intelligence (WISC-V) | 0 | 3 | 3 | 60 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline, month 12, and month 24 for TRIAL Participants. The WISC-V will be administered and scored on tablets digitally using the Pearson Clinical Q-Interactive platform.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [HORIZON Intensive] General Intelligence (WISC-V) | 0 | 2 | 2 | 60 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline and month 24 for HORIZON Intensive participants. The WISC-V will be administered and scored on tablets digitally using the Pearson Clinical Q-Interactive platform.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [PATHWAYS TRIAL] Inhibition, shifting, verbal fluency (D-KEFS) | 0 | 3 | 3 | 30 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline, month 12, and month 24 for TRIAL Participants. The D-KEFS will be administered and scored on a mixture of Q-Interactive and paper.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [HORIZON Intensive] Inhibition, shifting, verbal fluency (D-KEFS) | 0 | 2 | 2 | 30 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline and month 24 for HORIZON Intensive participants. The D-KEFS will be administered and scored on a mixture of Q-Interactive and paper.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |

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| [PATHWAYS TRIAL] Memory: visual recognition, verbal recall (CHAMP) | 0 | 3 | 3 | 35 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline, month 12, and month 24 for TRIAL Participants.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [HORIZON Intensive] Memory: visual recognition, verbal recall (CHAMP) | 0 | 2 | 2 | 35 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline and month 24 for HORIZON Intensive participants.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [PATHWAYS TRIAL] Memory validity profile (MVP) | 0 | 3 | 3 | 6 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline, month 12, and month 24 for TRIAL Participants.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [HORIZON Intensive] Memory validity profile (MVP) | 0 | 2 | 2 | 6 Minutes | <p>Research associates/assistants will conduct cognitive assessments at baseline and month 24 for HORIZON Intensive participants.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |
| [PATHWAYS TRIAL] Executive Functions at home (BRIEF) | 0 | 3 | 3 | 10 Minutes | <p>Parent/caregivers of TRIAL participants will complete the BRIEF2 at baseline, month 12 and month 24 with PATHWAYS research associates/assistants.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |

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| [HORIZON Intensive] Executive Functions at home (BRIEF) | 0 | 2 | 2 | 10 Minutes | <p>Parent/caregivers of HORIZON Intensive participants will complete the BRIEF2 at baseline and month 24 with PATHWAYS research associates/assistants.</p> <p>Cognitive assessments may also be delegated to trained psychologists or assistant psychologists in the gender services.</p> |

2. Clinical interventions

(Please complete for each intervention/procedure as follows)

1: Interventions/procedures to be received by each participant as part of the research protocol

2: Number of interventions/procedures which are part of standard care

3: Number of interventions/procedures which are additional to standard care

4: Total number of interventions/procedures

5: Average time taken per intervention/procedure (minutes, hours or days)

6: Details of who will conduct the intervention/procedure and where it will take place

| 1 | 2 | 3 | 4 | 5 | 6 |
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| [Immediate GnRHa] DEXA scan | 3-5 | 0 | 3-5 | 10-30 minutes | Hip/spine DEXA scans will take place at the recruiting site (secondary care Endocrine clinic), by radiology staff at screening, month 12 and month 24 for Immediate GnRHa participants. Participants will complete annual follow up scans following end of treatment until the end of the funding period (5.5 years). The exact number of scans is dependent on when the participant joins the trial in relation to the study's duration. |
| [Delayed GnRHa] DEXA scan | 3-5 | 0 | 3-5 | 10-30 minutes | Hip/spine DEXA scans will take place at the recruiting site (secondary care Endocrine clinic), by radiology staff at screening, month 12 and month 24 for Delayed GnRHa participants. Participants will complete annual follow up scans following end of treatment until the end of the funding period (5.5 years). The exact number of scans is dependent on when the participant joins the trial in relation to the study's duration. |

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| [HORIZON Intensive] DEXA scan | 0 | 2 | 2 | 10-30 minutes | Hip/spine DEXA scans will take place at the recruiting site (secondary care Endocrine clinic), by radiology staff at baseline and month 24 for HORIZON Intensive participants. |
| [Immediate GnRHa] Bone Age X-Ray | 1-3 | 0 | 1-3 | 10 minutes | X-ray Bone Age X-Rays of the non-left hand and wrist will take place at the recruiting site, by radiology staff. Scans at months 12 and 24 are optional for the immediate GnRHa group. |
| [Delayed GnRHa] Bone Age X-Ray | 1-3 | 0 | 1-3 | 10 minutes | X-ray Bone Age X-Rays of the left hand and wrist will take place at the recruiting site, by radiology staff. Scans at months 12 and 24 are optional for the delayed GnRHa group. |
| [HORIZON Intensive] Bone Age Scan | 0 | 1 | 1 | 10 minutes | X-ray Bone Age X-Rays of the non-left hand and wrist will take place at the recruiting site, by radiology staff. Bone Age Scans will be at baseline for HORIZON Intensive participants. |
| [Immediate GnRHa] Tanner's Staging Assessment | 1-4 | 0 | 1-4 | 15 minutes | Tanner staging assessments will be performed by qualified, delegated physicians at the recruiting site in the presence of a chaperone at screening. Assessments will be repeated at the baseline visit if >3 months has elapsed. Tanner staging is optional at months 12 and 24 for immediate GnRHa participants. |
| [Delayed GnRHa] Tanner Staging Assessment | 1-4 | 1 | 2-4 | 15 minutes | Tanner staging assessments will be performed by qualified, delegated physicians at the recruiting site in the presence of a chaperone at screening. Assessments will be repeated at the baseline visit if >3 months has elapsed. Month 12 Tanner staging for the delayed group is required prior to intervention. Tanner staging is optional at month 24 for delayed GnRHa participants. |

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| [HORIZON Intensive] Self-reported Tanner Staging | 0 | 2 | 2 | 2 minutes | Site staff will present CYP with a sex-specific pubertal self-assessment questionnaire. Birth registered females will be asked to choose the most appropriate breast and pubic hair Tanner stage. Birth registered males will be asked to choose the most appropriate genital and pubic hair Tanner stage. |
| [Immediate GnRHa] Self-reported Tanner staging | 0 | 1-4 | 1-4 | 2 minutes | Site staff will present CYP with a sex-specific pubertal self-assessment questionnaire at the same timepoints as the Tanner staging assessment. Birth registered females will be asked to choose the most appropriate breast and pubic hair Tanner stage. Birth registered males will be asked to choose the most appropriate genital and pubic hair Tanner stage. |
| [Delayed GnRHa] Self-reported Tanner staging | 0 | 2-4 | 2-4 | 2 minutes | Site staff will present CYP with a sex-specific pubertal self-assessment questionnaire at the same timepoints as the Tanner staging assessment. Birth registered females will be asked to choose the most appropriate breast and pubic hair Tanner stage. Birth registered males will be asked to choose the most appropriate genital and pubic hair Tanner stage. |
| [PATHWAYS TRIAL] Physical Examination | 2-6 | 0 | 2-6 | 30 minutes | For TRIAL participants, standard physical exam conducted by delegated physician at the recruiting site at screening; for subsequent examinations the extent will be at the discretion of the investigator. |
| [PATHWAYS TRIAL] Review of Systems | 4-5 | 0 | 4-5 | 15 minutes | Paediatric physical examination of cardiovascular system, respiratory system and abdomen for general health will be performed by delegated physicians at the recruiting site. Delayed GnRHa group participants will not undergo review of systems at month 6. |

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| [PATHWAYS TRIAL] Vital Signs | 5-6 | 0 | 5-6 | 15 Minutes | Research nurses at the recruiting site will obtain systolic and diastolic blood pressure, weight, height and BMI centile at each clinic visit. Delayed GnRHa group participants will not have vital signs taken at month 6. |
| [PATHWAYS TRIAL] Blood Tests | 5-6 | 0 | 5-6 | 10 Minutes | Research nurses or phlebotomists at the recruiting site will take bloods at each clinic visit for trial participants. Delayed GnRHa group participants will not have bloods taken at month 6. |
| [HORIZON Intensive] Blood Tests | 0 | 2 | 2 | 10 Minutes | Research nurses or phlebotomists at the recruiting site will take bloods at baseline and month 24 visits for HORIZON Intensive participants. |
| [PATHWAYS TRIAL] Urinalysis | 5-6 | 0 | 5-6 | 10 Minutes | Trial participants will provide urine samples for safety at each clinic visit. Delayed GnRHa group participants will not have to provide a urine sample for safety at month 6. |
| [HORIZON Intensive] Urinalysis | 0 | 2 | 2 | 10 Minutes | HORIZON Intensive participants will provide urine samples at baseline and month 24. |
| [PATHWAYS TRIAL] Pregnancy Test | 5-6 | 0 | 5-6 | 5 minutes | Participants of child bearing potential only are required to take a pregnancy test at each clinic visit. Delayed GnRHa group participants of child bearing potential will not have to take a pregnancy test at month 6. |
| [PATHWAYS TRIAL] Body Composition - Tanita Scale | 0 | 0-5 | 0-5 | 1 Minute | Optional body composition assessments using Tanita scales may be used to obtain detailed body mass percentages depending on investigator/participant preference at each clinic visit. |
| [HORIZON Intensive] Body Composition - Tanita Scale | 0 | 0-2 | 0-2 | 1 minute | Optional body composition assessments using Tanita scales may be used to obtain detailed body mass percentages depending on investigator/participant preference at baseline and month 24. |

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| [PATHWAYS CONNECT - Participants from PATHWAYS TRIAL] Structural/Functional MRI Scan | 0 | 3 | 3 | 60 minutes | MRI scans for PATHWAYS CONNECT participants recruited from PATHWAYS TRIAL will be conducted by researchers based at the Centre for Neuroimaging at KCL at baseline, month 12 and month 24. |
| [PATHWAYS CONNECT - Participants from PATHWAYS HORIZON Intensive] Structural/Functional MRI Scan | 0 | 2 | 2 | 60 minutes | MRI scans for PATHWAYS CONNECT participants recruited from PATHWAYS HORIZON Intensive will be conducted by researchers based at the Centre for Neuroimaging at KCL at baseline and month 24. |

3. Will you withhold an intervention, medicine or procedure, which would normally be considered a part of routine care?

Yes No

4. What are the potential risks and burdens for research participants and how will you minimise them?

Potential risks and burdens have been carefully considered in the study design.

1. Medical Risks from the Study Drug (GnRHa)

All participants will receive the study drug, either immediately or after a one-year delay. GnRHa is licensed for use in children with precocious puberty, but its use in gender incongruence is off-label. Side effects include mood changes, hot flushes, weight gain, fatigue, headaches, and reduced bone density. Rare but serious events include allergic reactions, seizures, and idiopathic intracranial hypertension.

To mitigate risks:

- Participants undergo medical screening before enrolment.
- Monitoring includes blood tests, physical exams, and bone scans.
- Side effects are documented and addressed promptly, in line with Good Clinical Practice.

2. Physical Examinations for Puberty Staging

Pubertal staging is essential to determine eligibility and timing for the study drug. These exams may be distressing.

To reduce discomfort:

- Multiple trained staff will perform assessments, offering choice.
- Trauma-informed approaches ensure sensitivity and respect.

3. Psychological and Emotional Burdens

The study involves discussions and assessments related to gender identity, mental health, and body image, which may be challenging.

To support participants:

- Questionnaires are age-appropriate and validated in similar populations, including PATHWAYS and HORIZON.
- The number of questionnaires is limited to domains identified by young people and families.
- Research staff are available during and after assessments to provide support and activate risk protocols.

4. Risk Management and Mental Health Support

Mental health support is integrated into the study.

- The NHS Gender Service continues care throughout the trial.
- High-risk behaviours, such as self-harm, are co-managed with CAMHS.
- In emergencies, the team liaises with CAMHS and other services.
- Researchers monitor mental health and escalate concerns. All staff receive Level 3 safeguarding training and have daily access to a Principal Investigator. Safety concerns are reviewed and, if needed, shared with clinical teams.

5. Practical and Time Commitments

Participation involves multiple visits over two years, including clinical appointments, scans, blood tests, and assessments.

To support engagement:

- Flexible scheduling and remote options are offered.
- Research assessments are coordinated with clinical visits.

- Travel expenses are reimbursed, and participants receive vouchers.

6. MRI Scanning (PATHWAYS CONNECT)

Some participants will undergo MRI brain scans, which may cause anxiety due to the enclosed space and noise.

To ease this process:

- Participants are screened for MRI suitability.
- A mock scanner and virtual reality tools help young people prepare.
- Scans are kept brief, with breaks and communication tools provided.

7. Data Privacy and Confidentiality

Participants will share sensitive personal information.

To protect privacy:

- Data is stored securely and anonymised.
- Only authorised personnel access identifiable data.
- All procedures comply with GDPR and NHS data protection regulations.

8. Randomisation and Delayed Treatment

Participants are randomly assigned to immediate or delayed treatment groups. The delay may be disappointing.

To address this:

- Randomisation is explained clearly during consent.
- All participants receive equal care and monitoring.
- The delayed group will access treatment after one year if clinically appropriate. Risk management applies equally.

9. Fertility Considerations

GnRHa may impact future fertility, though long-term effects are unclear. Discussions around fertility preservation may be sensitive.

To support informed decisions:

- Fertility options are discussed in a developmentally appropriate way.
- Participants and families are given time and support to consider choices.

10. Support for Participants Who Change Their Minds

Participants may reconsider treatment during the study.

To ensure autonomy:

- Young people are reminded they can withdraw at any time without affecting clinical care.
- Those who withdraw continue to receive support from the NHS Gender Service and other providers.

Finally, a placebo-controlled, double-blind design is not feasible because puberty suppression causes visible changes that participants would quickly notice, making it impossible to conceal treatment allocation. Instead, the trial compares starting treatment immediately versus after a one-year delay, allowing researchers to assess both short- and medium-term effects. This design enables measurement of psychological, physical, and cognitive outcomes, including changes in mental health and bone development. It also reflects real-world clinical care and avoids unnecessary procedures like sham injections. The approach is ethically sound and designed to provide meaningful evidence on the timing and impact of puberty suppression.

5. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

Yes No

5a. If yes, please give details of procedures in place to deal with these issues.

The PATHWAYS Trial includes questionnaires and interviews that explore sensitive topics such as gender identity, body image, mental health, self-harm, suicidal thoughts, trauma, eating behaviours, and sexual attraction. These topics may be distressing or upsetting for some participants, particularly given the age range (under 16) and the complex experiences of many CYP attending gender services.

To manage this, all measures have been reviewed by young people and parents for acceptability. Participants are supported by researchers to answer questions they find difficult.

There is a clear protocol for managing disclosures of risk or harm. If a participant discloses information suggesting they or someone else is at risk (e.g. self-harm, abuse, criminal activity), the researcher will follow safeguarding procedures. This includes informing the clinical team and, where necessary, liaising with local safeguarding services. Participants and parents are informed of these limits to confidentiality in the Participant Information Sheet.

All researchers receive Level 3 safeguarding training and have daily access to Principal Investigators with clinical expertise. Weekly team meetings provide space to discuss concerns and ensure staff wellbeing. Researchers also hold honorary NHS contracts or research passports, giving them access to NHS support systems.

The Gender Service leads on risk management throughout the trial. All participants undergo a baseline risk assessment, and safety

plans are developed for those at higher risk. The service liaises with CAMHS, social care, and other agencies as needed. Any disclosures made during research activities are shared with the clinical team to ensure continuity of care and appropriate follow-up.

6. What arrangements are being made for continued provision of the investigational medicinal product for participants, if appropriate, once the research has finished? If the intention is to not provide IMP to participants when the trial has completed, this must be clearly justified.

Continued access to GnRHa for individuals with diagnosed gender dysphoria whose treatment has been initiated and maintained in line with the PATHWAYS clinical trial protocol will be subject to:

EITHER

- GnRHa treatment eligibility under routine NHS commissioned gender care as set out in a published (contemporary, nation-specific) clinical commissioning policy

OR

Eligibility under a separate commissioning statement which will set out the specific circumstances within which ongoing access to GnRHa might continue for those whose GnRHa treatment was initiated under the PATHWAYS clinical trial.

It has been agreed that, subject to the PATHWAYS clinical trial not identifying significant harm(s) such that ongoing access would be considered unsafe or unethical, a commissioning statement (or equivalent) will be published within each of the UK nations participating in the clinical trial to support, in addition to any routinely commissioned indications, post-trial access to GnRHa specifically for PATHWAYS clinical trial participants.

Under the commissioning statement, access will be supported where there is:

- ongoing assessment and participation in a tailored package of psychosocial care under the oversight of a specialist NHS gender service AND

- agreement between the individual (and / or their legal guardian, as age appropriate) and their NHS specialised gender service clinician that ongoing GnRHa treatment remains in their best interest AND

- a positive recommendation for continuation from the national multidisciplinary team (NMDT) (a NMDT review must be planned and undertaken on completion of the PATHWAYS clinical trial and then at least annually thereafter) AND

- there being a confirmed prescriber working as part of the extended clinical team within a commissioned NHS gender service

7. Will you inform the participants' General Practitioner that they are taking part in the trial? (and/or any other healthcare professional responsible for their care).

Yes

No

8. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

Yes

8a. If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

Participants recruited into PATHWAYS TRIAL may be participating in PATHWAYS HORIZON (IRAS ref: 350909), the large observational study component of the PATHWAYS programme of research, at the time of their recruitment. Participants that are enrolled into PATHWAYS TRIAL from PATHWAYS HORIZON will end their participation in the latter. All participants enrolled into HORIZON Intensive will first participate in PATHWAYS HORIZON, as they will be broadly matched by key characteristics to participants in PATHWAYS TRIAL.

9. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?

The PATHWAYS Trial is committed to inclusivity and ensuring that no eligible participant is excluded due to language barriers or communication needs. The trial includes children and young people (CYP) aged under 16, many of whom may have neurodevelopmental conditions like autism. The protocol outlines several measures to support understanding and informed participation.

For participants who do not adequately understand English, where appropriate, interpreters will be arranged through NHS services at each site. Where needed, participant-facing documents will be translated centrally to ensure consistency and accuracy.

For CYP with special communication needs, including those with neurodivergence, the study team will provide bespoke formats of information. This includes visual supports, simplified text, and audio recordings. Researchers will be trained to assess understanding and adapt communication accordingly. CYP will be asked to explain their understanding of the study in their own words, and a

checklist will be used to ensure comprehension.

Where there is uncertainty about a CYP's capacity to assent or consent, a formal mental capacity assessment will be conducted by a qualified clinician (e.g. paediatrician, psychiatrist, or senior psychologist) or a trained researcher with an honorary NHS contract. This assessment follows the Mental Capacity Act framework. However, it is unlikely that CYP will be considered clinically eligible if there is a question about their capacity to understand the potential benefits and harms of GnRHa and puberty suppression. Researchers will also check at each in person visit with parents or guardians whether there has been any change in the CYP's capacity and repeat assessments if needed. Any concerns will be immediately communicated to the Care Team in the Gender Service. These procedures ensure that all participants are supported to make informed decisions and that their inclusion is ethically sound and legally compliant.

C. Transparency

1. How do you intend to report and disseminate the results of the study?

- Peer reviewed scientific journals
- Internal report
- Conference presentation
- Publication on website
- Other publication
- Submission to regulatory authorities
- Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- No plans to report or disseminate the results
- Other

2. How will you enable sharing of study data with others?

In line with the principles of research transparency and the collaborative nature of scientific inquiry, the PATHWAYS research team is committed to making anonymised primary research data available for future analysis, subject to appropriate safeguards. Participants will be informed during the consent process that anonymised data collected during the study may be shared with other researchers for secondary analysis, meta-analysis, or to inform future research. This is to maximise the value of their contribution, facilitate independent verification of results, and support the development of evidence-based care for children and young people with gender incongruence.

Following completion of the study and publication of the primary results, anonymised datasets may be made available to external researchers upon written application to the Chief Investigator. Applications will be reviewed by the Study Management Group, chaired by the Chief Investigator. Any data sharing will be governed by a formal Data Sharing Agreement between the sponsor and the requesting institution, ensuring that data are used responsibly, securely, and in accordance with ethical and legal standards. All shared data will be fully anonymised in accordance with the UK GDPR and Data Protection Act 2018, such that individuals cannot be identified by the research team or any third party. Identifiable data will not be shared. The anonymisation process will include removal of direct identifiers and application of appropriate safeguards to prevent re-identification.

The full study protocol will be published in an open-access journal, providing transparency and enabling other researchers to understand the context and methodology of the PATHWAYS Trial, CONNECT, and HORIZON Intensive studies.

3. How will you enable sharing of tissue samples and associated data with others?

Tissue samples will be collected as part of safety assessments throughout the trial. These samples will be tested and disposed of as per local procedures and not retained for any period or for future research.

4. How and when will you inform participants of the study results?

If there will be no arrangements in place to inform participants please justify this.

We are committed to ensuring that participants, their families, and the wider community are informed of the study results in a timely, accessible, and meaningful way. The findings of the PATHWAYS study are of significant interest to the trans community, healthcare professionals, and the public.

Once peer-reviewed manuscripts are accepted for publication, we will produce accessible, easy-read summaries of the findings. These will be developed in collaboration with our lived experience Advisory Groups and communications specialists to ensure clarity, relevance, and sensitivity. These summaries will be made available through multiple channels, including:

- The NHS Children and Young People's Gender Service (CYPGS)
- The PATHWAYS study website
- Printed copies available at participating clinics
- Direct email or post to participants who opt in to receive results

We will offer printed summaries and ensure that participants are informed during the consent process about how they can choose to receive results.

We will also work with the Science Media Centre to support accurate and responsible media coverage of the findings. In addition, our Study Advisory Groups will be invited to co-author publications, present at conferences, and contribute to public engagement activities.

To further enhance understanding, we will collaborate with our Study Advisory Groups and specialist communications team to develop supplementary materials such as infographics, animations, and short videos, tailored for different audiences including young people and families.

These dissemination plans will be described in the Participant Information Sheets, and participants will be asked how they would prefer to receive study results.

5. Point of Contact for Publication

Chief Investigator

D. Scientific and Statistical Review

1. How has the scientific quality of the trial been assessed?

- Independent external review
- Review within a company
- Review within a multi-centre research group
- Review within the Chief Investigator's institution or host organisation
- Other

2. Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:

As part of the grant application, an independent scientific review was conducted by the funding body. The funding body has reviewed the protocol submitted within this application and approved it. The scientific quality of the trial has also been reviewed within KCL by the Senior Statistician, who is a professor of Medical Statistics and Trials Methodology and theme lead for Clinical Trials Methodology at the Department of Biostatistics and Health Informatics.

3. How have the statistical aspects of the research been reviewed?

- Review by independent statistician commissioned by funder or sponsor
- Other review by independent statistician
- Review by company statistician
- Review by a statistician within the Chief Investigator's institution
- Review by a statistician within the research team or multi-centre group
- Review by educational supervisor
- Other review by individual with relevant statistical expertise

4. In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

Title

Prof

Forename/Initials

██████

Department

Biostatistics & Health Informatics

Institution

Institute of Psychiatry, Psychology and Neuroscience

Street

16 De Crespigny Park

City

London

Country

United Kingdom

Post code

SE5 8AB

Email

██████@kcl.ac.uk

Telephone

██████

5. How was the sample size decided upon?

The anticipated sample size for TRIAL is approximately 226 participants. This sample size is based on the expected eligible clinic prevalence of gender-related distress, allowing for sufficient power to estimate the posterior distributions of treatment effects and to detect meaningful differences and associations in the primary and secondary outcomes.

Using simulations, it was determined that with 226 participants the trial would have 91% power with a standardised effect size (SES) of 0.525. For the primary outcome, the SES of 0.525 means a difference of 5.25 points on the standardised KIDSCREEN-10 t-score, where the standard deviation is 10 for all t-scores at all timepoints.

If recruitment is lower than expected, power will be lower to detect the same SES. If only 150 participants are recruited, the trial would still have around 80% power to detect the SES of 0.525. Recruitment above 150 has power between 80 and 90% to determine an SES of 0.525.

The sample size for Horizon Intensive will be 300. These 300 participants will, in general, be matched to participants in the trial based on the stratifying factors of the trial randomisation. With 300 participants, there is sufficient power to test the intensive participants against those participants in the trial immediate arm. We will be able to detect a SES of 0.42 with around 90% power (300 vs 112). We will have 90% power to detect a 0.32 SES for intensive participants to be tested against the whole trial population (300 vs 226).

The planned sample size for PATHWAYS CONNECT is 250 participants; 150 from TRIAL (75 per arm), 100 from HORIZON Intensive. We are assuming a small-to-medium effect size (partial $\eta^2=0.03$) and a conservative rate of dependent variable autocorrelation within subject (0.5, other studies in adolescents and late childhood have shown values >0.7).

F. Ionising Radiation

1. Does the study involve exposures to radioactive materials?

Yes No

2. Does the study involve other diagnostic or therapeutic ionising radiation?

Yes No

3. Has the trial been authorised by a Clinical Radiation Expert (CRE) and a Medical Physics Expert (MPE)?

Yes

No

4. What are the risks associated with ionising radiation exposures within the trial?

This study requires exposures to ionising radiation which are detailed in A1 and B1. Some of the exposures required by the study are additional to routine clinical care.

Immediate GnRHa (Trial): 2 x Dexa Hip/Spine (+ 2 optional) + 2 x Left Hand/Wrist (+ 2 optional): 78.6uSv -157.2uSv
Delayed GnRHa (CONNECT): 2 x Dexa Hip/Spine (+ 2 optional) + 2 x Left Hand/Wrist (+ 2 optional): 78.6uSv -157.2uSv
HORIZON Intensive: 2 x Dexa Hip/Spine + 2 x X-ray Left Hand/Wrist: 78.6uSv

The total protocol dose is up to 0.16 mSv (Trial / CONNECT) or 0.08mSv (HORIZON Intensive), assuming all participants remain in the three studies. This is equivalent to a approximately 1 month's of average natural background radiation in the UK.

Ionising radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study, adjusted for age and sex (HPA-CRCE-028), is up to 0.002% (Female chest 10-19 years; 12%/Sv), which is very low. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

Extra information provided by the application regarding MRI scanning procedures in PATHWAYS CONNECT:

The MRI scanning in PATHWAYS CONNECT involves use of software which is outside of the MRI scanner's formal CE marked approval. This software reconstructs underlying data the scanner collects into an interpretable image. These non-CE marked modifications are stringently tested and comply with all relevant safety limits and guidelines.

G. Tissue

1. List the human biological material/tissue samples which will be removed and/or stored as part of the research

The PATHWAYS research programme involves the collection of the following human biological materials for safety monitoring and research purposes. These apply to both the PATHWAYS Trial and HORIZON Intensive cohorts (optional), with some differences in frequency and scope of collection.

1. Blood Samples

Purpose: Hormonal profiling, safety monitoring, and assessment of physical health.

Tests include:

Hormonal assays: Follicle Stimulating Hormone (FSH), Luteinising Hormone (LH), Oestradiol, Testosterone, Prolactin

Safety panels: Full Blood Count, Liver Profile, Renal Profile, Lipid Profile, Bone Profile

Other markers: Ferritin, Thyroid Stimulating Hormone (TSH), Free T4, Vitamin D

Timing:

PATHWAYS Trial: Screening, baseline, and follow-up visits (3–6 month intervals)

HORIZON Intensive: Baseline and 24-month endpoint only

2. Serum Pregnancy Tests

Purpose: To confirm non-pregnancy status in participants of childbearing potential prior to administration of GnRHa.

Timing: At screening and baseline for all relevant participants.

3. Urine Samples

Purpose: Pregnancy testing and urinalysis for safety monitoring.

Tests include: Protein, glucose, blood, ketones, nitrites, leukocyte esterase, and microscopic examination if indicated.

Timing:

PATHWAYS Trial: Screening and follow-up visits

HORIZON Intensive: Baseline and 24-month endpoint

5. If you are obtaining existing tissue samples, will there be consent in place?

Select..

6. What will happen to the samples at the end of the research?

- Transfer to research tissue bank
- Storage by research team pending ethical approval for use in another project
- Storage by research team as part of a new research tissue bank
- Storage by research team of biological material which is not “relevant material” for the purposes of the Human Tissue Act
- Disposal in accordance with the Human Tissue Authority’s Code of Practice
- Other
- Not yet known

H. Recruitment and Informed Consent Procedure

1. How will potential participants be identified?

Potential participants for the PATHWAYS Trial will be identified through NHS England’s Children and Young People’s Gender Services (CYPGS). Identification will be carried out by the clinical care team responsible for the young person. Only children and young people (CYP) assessed as clinically eligible for gonadotropin-releasing hormone analogues (GnRHa) will be considered. This eligibility is determined through a two-stage process: first by the local CYPGS team, then confirmed by the national multidisciplinary team (NMDT), ensuring consistency and adherence to national commissioning policy.

The CYPGS NMDT is a multidisciplinary panel comprising senior clinicians from the NHS Children and Young People’s Gender Service. It reviews comprehensive documentation submitted by treating clinicians—including psychosocial assessments, physical health evaluations, and educational and safeguarding reports—to ensure consistent, holistic decision-making across services. The NMDT provides assurance and a recommendation regarding appropriateness for trial eligibility screening, although the final decision remains with the referring clinician who can opt not to provide GnRHa in instances where the national MDT has given a favourable opinion that the CYP can be considered eligible for this treatment. The eligibility criteria have been developed collaboratively with members of the NMDT, including the Chair and Service Director of the National Providers Network.

The process of determining eligibility is multidisciplinary and involves structured discussions between the CYP, their parent(s)/guardian(s), and clinicians, including paediatric endocrinologists and mental health professionals. These discussions are documented in clinical records and include the CYP’s understanding of treatment, their preferences, and the views of their parent(s)/guardian(s). Information is provided in accessible formats tailored to the CYP’s cognitive and learning needs, including visual aids and audio recordings where appropriate.

CYP and families who express interest in puberty suppression are informed early that access to this intervention is only available through the PATHWAYS Trial. Once eligibility is confirmed, the clinical team introduces the research opportunity and refers the CYP to the PATHWAYS research team. The research team provides detailed information and obtains informed assent/consent. This ensures that only CYP under CYPGS care and deemed clinically appropriate for GnRHa are approached, embedding identification within routine care. The research team will not influence recruitment numbers or rates.

Participants for PATHWAYS HORIZON Intensive will be identified from the existing PATHWAYS HORIZON observational cohort study (IRAS: 350909), which includes CYP attending CYPGS who have consented to be contacted for future research. Identification will be conducted by the PATHWAYS research team under arrangements with the responsible NHS care organisations.

HORIZON Intensive participants will be selected using matching criteria aligned with the PATHWAYS Trial cohort, including clinical centre, birth-registered sex, age, pubertal stage (Tanner), and presence of neurodevelopmental traits. This creates a comparison group of CYP not receiving GnRHa but otherwise similar to those in the trial. Matching is essential to compare outcomes between treated and untreated groups.

To ensure balanced recruitment, the research team will use the HORIZON database to identify eligible participants. After confirming with the clinical service that these individuals are not seeking or eligible for GnRHa, they will be approached directly by the research team. Initial contact will be made via an information sheet, followed by discussion in person or via video call. Recruitment will be timed to coincide with annual assessments to minimise participant burden.

Participants for PATHWAYS CONNECT will be identified from those enrolled in both the PATHWAYS Trial and HORIZON Intensive. For Trial participants, CONNECT will be introduced alongside the main trial, and consent must be obtained before randomisation to allow for baseline MRI scanning. This ensures neuroimaging data are collected before GnRHa intervention begins.

For HORIZON Intensive participants, CONNECT will be discussed at the same time as HORIZON Intensive. This integrated approach ensures participants are fully informed and can consent to multiple components if they wish. Participants must be willing to travel to London (King’s College London) for MRI scanning and meet MRI safety criteria.

All identification and referral processes will be clearly explained in participant materials. It will be made clear that participation in CONNECT is entirely voluntary. The research team will ensure all contact complies with NHS and research governance policies, including data protection and confidentiality. Where referrals are made by clinical teams, this will be clearly stated in communications.

2. What resources will be used for recruitment?

Recruitment to the PATHWAYS Programme—including the PATHWAYS Trial, HORIZON Intensive, and CONNECT studies—will be supported by a range of carefully designed resources to ensure that potential participants and their families are fully informed and supported throughout the recruitment process. These resources are tailored to the needs of children and young people (CYP) with gender incongruence and their families, and are delivered in formats that are accessible, inclusive, and developmentally appropriate. Participant Information Sheets (PIS)

Each study within the PATHWAYS Programme has a dedicated Participant Information Sheet (PIS). These include:

PATHWAYS Trial PIS
HORIZON Intensive PIS
CONNECT PIS
Parent/Guardian PIS

These documents are written in plain English and have been co-developed with the PATHWAYS Engagement Advisory Group, which includes young people with lived experience, parents, and carers. Where needed, alternative formats (e.g. large print, audio, visual aids) will be made available to support CYP with different learning styles or communication needs.

PIS documents will be provided:

In clinic: handed out during routine CYPGS appointments by the clinical team
By post or email: for families who prefer to review materials at home
During information sessions: led by the research team or endocrine specialists
Via secure online platforms: including the PATHWAYS website and Medrio ePRO system

PATHWAYS Programme Overview Materials

General information about the PATHWAYS Programme is available through:

The NIHR and King's College London websites

The PATHWAYS study website

These materials are intended to raise awareness of the research programme and provide a consistent message across all recruitment sites.

Researcher-Led Information Sessions

In addition to written materials, recruitment will be supported by:

In-person or virtual information sessions led by PATHWAYS researchers
Q&A sessions for CYP and families to ask questions in a supportive environment
Follow-up calls or emails to clarify any outstanding questions
Wherever additional information is requested outside the researchers' expertise, they will refer to a relevant expert: Principal Investigator, paediatric endocrinology or clinician caring for the CYP

These sessions are particularly important for CONNECT and HORIZON Intensive, where participation involves additional assessments such as MRI scans or cognitive testing.

Recruitment Pathways

All recruitment will occur within the NHS setting, and no participants will be approached via social media, radio, or public advertising. Identification and initial approach will be made by the direct care team (CYPGS clinicians), with referral to the research team only after clinical eligibility is confirmed. This ensures that all contact is appropriate, ethical, and aligned with NHS governance.

3. Will identification of potential participants involve access to identifiable information?

Yes No

3a. If yes, describe what measures will be in place to confirm that access to this information will be lawful.

Identification of potential participants for the PATHWAYS Programme—including the PATHWAYS Trial, HORIZON Intensive, and

CONNECT—will involve access to identifiable information such as names, dates of birth, NHS numbers, and clinical records. This access is necessary to determine clinical eligibility, match participants across study arms, and ensure appropriate and ethical recruitment. The following measures will be in place to ensure that access to this information is lawful, proportionate, and compliant with data protection legislation and research governance frameworks.

1. Access by the Direct Care Team

Initial identification of potential participants will be carried out exclusively by members of the CYP's existing clinical care team within the NHS England Children and Young People's Gender Services (CYPGS). These clinicians already have lawful access to patient records as part of their routine care responsibilities. This includes paediatric endocrinologists, psychologists, psychiatrists, and other multidisciplinary team members involved in the assessment and care of CYP with gender incongruence.

For the PATHWAYS Trial, clinical eligibility for GnRHa treatment is determined through a structured process involving both the local CYPGS team and the national multidisciplinary team (NMDT). This process is embedded within routine clinical care and does not require additional consent for access to records. The NMDT reviews comprehensive documentation submitted by clinicians, including biopsychosocial assessments, education and safeguarding reports, and individual impact assessments. These reviews are conducted via a secure digital platform and are part of the standard NHS pathway for determining eligibility for endocrine intervention.

2. Referral to the Research Team

Only after a CYP has been confirmed as clinically eligible for GnRHa will they be referred to the PATHWAYS research team. At this point, the research team will be provided with limited identifiable information (e.g. name, date of birth, contact details) solely for the purpose of discussing potential participation in the study. This referral is made by the clinical team, and the research team will only access clinical records when CYP have indicated they are interested in the trial. Researchers accessing clinical records will all have honorary clinical contracts with the relevant service.

For HORIZON Intensive and CONNECT, participants are identified from the PATHWAYS HORIZON cohort, where prior consent has been obtained to be contacted about future research. The research team accesses this information under a data-sharing agreement with the responsible NHS organisation, and only for participants who have explicitly agreed to be re-contacted.

3. Lawful Basis and Data Protection Compliance

All access to identifiable information is conducted in accordance with the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018. The lawful basis for processing is Article 6(1)(e) (task in the public interest) and Article 9(2)(j) (research purposes with appropriate safeguards).

Data minimisation principles are strictly followed. Only the minimum necessary identifiable information is accessed, and only by staff with appropriate training and authorisation. All data are stored securely, with access restricted to named individuals on the delegation log.

4. Oversight and Monitoring

The study is managed by the King's Clinical Trials Unit (KCTU), which ensures compliance with Good Clinical Practice (GCP) and data protection standards. All data access and handling procedures are documented in the study protocol and Standard Operating Procedures (SOPs). Regular monitoring visits will be conducted by the Kings Health Partners Clinical Trials Office (KHP-CTO) to ensure adherence to these standards and procedures.

4. Who will be approaching potential participants and who will be obtaining informed consent?

[TRIAL]

Informed consent will be obtained from parents and assent from CYP by a delegated, medically qualified investigator, adhering to GCP principles at all times. Where possible, the key clinician at the CYPGS with oversight of the CYPs care up to that point will join the assent/consent appointment to support the CYP and their parent/legal guardian, and to ensure they have sufficient opportunity to ask and have questions answered fully. The possibility of fertility preservation will be discussed with each CYP and their wishes to access this prior to GnRHa treatment will be recorded. The investigator taking informed assent/consent will check that these are present prior to taking informed assent/consent.

[HORIZON Intensive]

Research associates/assistants (RAs) based at UK Gender Services will approach HORIZON participants identified by the central team as matching in characteristics to Trial participants. RAs will take informed consent from participants with support from a delegated medical practitioner.

[CONNECT]

Research associates/assistants (RAs) based at UK Gender Services will approach potential CONNECT participants from the HORIZON cohort at the same time as approaching for HORIZON Intensive. Likewise, RAs will approach potential CONNECT

participants at the same time as enrolling in PATHWAYS Trial. RAs will take informed consent from participants with support from a delegated medical practitioner.

5. How, when and where will informed consent be obtained?

Overview

Informed assent and/or consent will be obtained for all participants in the PATHWAYS Trial, HORIZON Intensive, and CONNECT studies. The process will be tailored to the developmental stage, cognitive needs, and legal status of each child or young person (CYP), and will involve their parent(s) or legal guardian(s) where appropriate. The process will follow Good Clinical Practice (GCP) and ethical standards, ensuring that participation is fully informed, voluntary, and documented.

Participant-facing materials—including Participant Information Sheets (PIS), consent and assent forms—have been reviewed and co-developed with the PATHWAYS Engagement Advisory Groups, which include young people with lived experience, parents, and carers. Their feedback has shaped the language, format, and accessibility of materials to ensure they are age-appropriate, inclusive, and sensitive to the needs of CYP with gender incongruence.

[PATHWAYS TRIAL]

How:

Informed assent (for CYP under 16) and informed consent (for parents/legal guardians) will be obtained using paper forms. These forms will be signed by the participant and at least one parent/legal guardian, and counter-signed by a medically qualified investigator or delegated sub-investigator. The process will include a structured discussion with a clinician, supported by written and visual materials tailored to the CYP's cognitive and learning style. A checklist will be used to confirm understanding of key concepts, including the risks and benefits of GnRHa, fertility preservation, and long-term implications.

When:

Consent will be obtained only after the CYP has been assessed as clinically eligible for GnRHa by both the local clinical team and the national multidisciplinary team (NMDT). This occurs after a series of clinical consultations and information sessions. Consent will be sought after the CYP and their family have had time to review the PIS and discuss the study with clinicians and the research team. Consent will not be obtained at the same time as eligibility is discussed, to ensure voluntariness. CYP will have the opportunity to speak with the clinical and research team separately from their parents to address any independent questions.

Where:

Consent will be obtained during a scheduled clinic appointment at the NHS Gender Service (CYPGS). This will take place in person at a regional Endocrine Centre.

By whom:

Assent/consent will be obtained from a medical doctor in the research team and typically also attached to the clinical service. They may be accompanied by a researcher who can answer further questions about the research protocol and/or by the CYP's clinical keyworker who will know the issues and questions raised by the CYP and their parent. Assent/consent from CYP and parents will typically be taken at the same time unless there is any concern about the lack of voluntary agreement, at which point, they may be seen separately.

Safeguards for Vulnerable Participants:

CYP with neurodevelopmental or other conditions/background factors that may alter their access to typical forms of information-sharing will be supported with adapted materials (e.g. visual aids, simplified text, audio recordings). Clinicians will assess capacity to assent/consent and ensure that the CYP's views are heard independently of parental influence. Where only one parent is present, the reason will be documented. The process will be paced to allow time for reflection and questions.

[HORIZON INTENSIVE]

How:

Informed assent/consent will be obtained using paper forms. The process will be led by a PATHWAYS researcher, who will explain the study using the PIS and answer any questions. The forms will be signed by the CYP (if under 16, assent) and their parent/legal guardian (consent), or by the CYP alone if aged 16+ and deemed competent.

When:

Consent will be obtained after the participant has already enrolled in the PATHWAYS HORIZON observational cohort and has agreed to be contacted about further research. Recruitment to HORIZON Intensive will typically occur near an annual assessment timepoint to minimise burden. Participants will be given time to review the information before deciding.

Where:

Consent may be obtained in person at a CYPGS clinic

Safeguards for Vulnerable Participants:

As with the Trial, materials will be adapted for CYP with additional needs. Researchers will be trained in communicating with neurodiverse participants and will ensure that consent is informed and voluntary. The process will be documented in the study records.

[PATHWAYS CONNECT]

How:

Informed assent/consent for CONNECT will be obtained using a separate PIS and consent form, in addition to those used for the Trial or HORIZON Intensive. The process will include explanation of MRI procedures, potential risks (e.g. discomfort, incidental findings), and the voluntary nature of participation. Participants will be asked to confirm their willingness to travel to London for MRI scans.

When:

For Trial participants, CONNECT consent will be obtained prior to randomisation, to allow for baseline MRI scanning. For HORIZON Intensive participants, CONNECT will be introduced at the same time as HORIZON Intensive, and consent obtained concurrently.

Where:

Consent will be obtained in clinic. MRI scans will take place at King's College London.

Safeguards for Vulnerable Participants:

MRI safety screening will be conducted, and participants will be supported with mock scanner sessions or virtual reality tools to reduce anxiety. The consent process will emphasise that participation in CONNECT is optional and does not affect involvement in the main study.

6. How long will potential participants (or their legal representative) be given to decide whether to participate?

There is no upper limit for potential participants or their legal representative to decide on whether to participate. Potential participants will be instructed to read the PIS with their parent/caregiver and encouraged to thoroughly discuss the information they have received about the trial with their parent/caregiver, as well as the GP if felt appropriate. Potential participants will be encouraged to ask the trial investigator any questions they have, discuss any concerns, or request further detail on any of the information they have received.

There is no lower limit on deciding whether to participate. At the point of consenting to the trial, participants will have undergone clinical eligibility screening where the requirements and eligibility for the trial is discussed.

7. How will it be assured that potential participants (or their legal representative) have understood the information and that consent is informed?

Ensuring that consent is fully informed, voluntary, and based on a clear understanding of the research is a central ethical and legal requirement of the PATHWAYS Trial, HORIZON Intensive, and CONNECT studies. This is particularly important given the complexity of the intervention (GnRHa for puberty suppression), the developmental stage of participants (under 16s), and the potential for long-term implications.

1. Clinical Foundation for Informed Consent

Before any approach is made by the research team, all potential participants undergo a rigorous clinical eligibility and readiness assessment conducted by the NHS Children and Young People's Gender Services (CYPGS). This includes:

A structured, multi-session process of information sharing and discussion with the CYP and their parent(s)/legal guardian(s)

Use of a detailed clinical checklist to assess understanding, capacity, and voluntariness

Documentation of direct quotes and summaries of discussions to evidence comprehension and decision-making

This process ensures that by the time a CYP is referred to the PATHWAYS Trial, they and their family have already had multiple opportunities to consider the intervention, ask questions, and reflect on the implications.

2. Assessment of Understanding and Capacity

For CYP under 16, the clinical team assesses Gillick competence using the following criteria:

- The ability to understand the nature, purpose, and potential consequences of the treatment and research
- The ability to retain and recall relevant information
- The ability to weigh up the advantages and disadvantages of participation
- The ability to communicate their decision clearly and consistently

This assessment is not a one-off event but a cumulative process, documented over time. Clinicians are required to hold both joint and one-to-one sessions with the CYP and their parent(s) to ensure that decisions are made freely and without coercion. Where a CYP is deemed Gillick competent, they may provide assent to participate in the trial. However, at least one person with parental responsibility must also provide consent. The views of both parties are documented separately to ensure clarity and transparency.

3. Research Consent Process

Once referred to the research team, informed assent/consent is obtained using a structured, multi-step process:

CYP and parents are provided with age-appropriate Participant Information Sheets (PIS), developed with input from the PATHWAYS Engagement Advisory Groups
Information is presented in multiple formats (written, visual, audio) and adapted to the CYP's cognitive and communication needs
The research team confirms understanding by asking open-ended questions and encouraging CYP to explain the study in their own words

A checklist is used to ensure that key topics have been covered, including:

- The purpose of the study
- What participation involves (e.g. randomisation, assessments, MRI scans)
- Potential risks and benefits
- The voluntary nature of participation and the right to withdraw
- The implications of GnRHa treatment, including fertility and long-term outcomes

Consent is only documented once the investigator is satisfied that the CYP and parent(s) have understood the information and are making an informed, voluntary decision.

4. Addressing Individual Needs

The PATHWAYS Programme recognises that many CYP referred to gender services may have neurodevelopmental or, learning difficulties, or communication needs or other experiences that alter their access to typical ways of sharing information. To ensure inclusivity and valid consent:

- Information is tailored to the CYP's developmental level and learning style
- Visual aids, simplified text, and audio recordings are used where appropriate
- Interpreters are provided for families with limited English proficiency
- Clinicians and researchers are trained in communicating with neurodiverse CYP and other groups that may require adaptations
- Reasonable adjustments are made to support understanding and participation

Where there is uncertainty about capacity or understanding, additional sessions are offered, and consent is delayed until the team is confident that the criteria are met.

5. Documentation and Oversight

All discussions are documented in the clinical record and research file, including:

- Dates of discussions
- Summary of topics covered
- Direct quotes from the CYP and parent(s)
- Confirmation of Gillick competence (where applicable)
- Signatures of the CYP, parent(s), and investigator

This documentation is part of the review for clinical eligibility. This documentation provides a clear audit trail and ensures that

consent is not only informed but demonstrably so.

8. What arrangements are in place to obtain informed consent from potential participants (or their legal representative) who do not speak English?

The PATHWAYS Programme is committed to ensuring equitable access to participation for all eligible children and young people (CYP) and their families. The study has put in place arrangements to support informed consent for participants and legal representatives who do not speak English where appropriate.

1. Identification of Language Needs

Language needs are identified early in the clinical pathway through the NHS Children and Young People's Gender Services (CYPGS). As part of routine clinical care, clinicians record the preferred spoken and written language of the CYP and their parent(s)/ legal guardian(s). This information is shared with the research team at the point of referral to ensure that appropriate language support is in place before any consent discussions occur.

2. Use of Professional Interpreters

Where verbal interpretation is required, professional, independent interpreters will be arranged through NHS-approved interpretation services. These interpreters:

- Are trained in medical and research terminology
- Are bound by confidentiality agreements
- Are not family members or friends of the participant
- Can be provided in person or via secure video or telephone platforms

Interpreters will be present during all key discussions, including:

- Explanation of the Participant Information Sheet (PIS)
- Consent/assent discussions
- Clarification of study procedures, risks, and rights

This ensures that participants and their families can ask questions and receive answers in their preferred language.

3. Translation of Written Materials

The Chief Investigator (CI) and sponsor will centrally coordinate the translation of participant-facing documents where appropriate and as the need arises. These include:

- Participant Information Sheets (PIS) for CYP and parents
- Consent and assent forms
- Translations will be carried out by certified medical translation services and reviewed for cultural appropriateness and clarity.
- Translated documents will be made available to all participating sites via a secure shared repository.
- Where a participant requires a language not yet available, the site PI will notify the CI, and a translation will be commissioned.

4. Ensuring Understanding and Valid Consent

To ensure that consent is informed and valid:

- The research team will confirm that the participant and/or parent has received the translated materials in advance and had time to review them
- During the consent discussion, the researcher will use open-ended questions (via the interpreter) to assess understanding
- Participants will be encouraged to explain the study in their own words
- Any misunderstandings will be clarified before consent is documented

5. Documentation and Oversight

- The use of interpreters and translated materials will be recorded in the consent form and source documents. This includes:
 - The name and organisation of the interpreter
 - The language used
 - Confirmation that the participant and/or parent received and understood the translated materials
 - Any additional support provided (e.g. visual aids)

6. Ethical Justification for Inclusion

The PATHWAYS Programme does not exclude participants based on language. The study recognises that CYP with gender

incongruence come from diverse linguistic and cultural backgrounds, and that equitable access to research is important for generalisability and fairness.

9. How will it be ensured that participants can withdraw their consent at any point?

It is stated in all participant information sheets and informed assent/consent forms provided to participants that they have the legal right to withdraw from PATHWAYS TRIAL/CONNECT/HORIZON Intensive at any time, without having to provide a reason for doing so, without their care in the gender service being negatively impacted as a result. If a participant chooses to withdraw from PATHWAYS TRIAL/CONNECT/HORIZON Intensive at any stage, a withdrawal form documenting the reason for withdrawal (if provided) will be completed, filed in the participants medical notes, and transcribed into the relevant EDC system. [For participants withdrawing from PATHWAYS TRIAL treatment, the primary care team at the gender service will develop a clinical care plan for coming off GnRHa treatment and detail next steps in the treatment pathway]

10. Please provide any further information, in relation to the procedure for recruitment and informed consent for the clinical trial, which has not been provided elsewhere.

n/a

11. Provide a clear indication of what the first act of recruitment will be.

PATHWAYS Trial

The first act of recruitment for the PATHWAYS Trial will be the identification of potentially eligible participants by the clinical care team within the NHS England Children and Young People's Gender Services (CYPGS). Specifically, this will occur after a CYP has been assessed as clinically eligible for puberty suppression using gonadotropin-releasing hormone analogues (GnRHa), following a structured, multidisciplinary process.

This clinical eligibility assessment includes:

Review by the local CYPGS team

Confirmation by the national multidisciplinary team (NMDT)

Completion of a detailed consent and capacity checklist (for under 16s), including documentation of understanding, voluntariness, and readiness

Only after this clinical process is complete will the CYP and their parent(s)/legal guardian(s) be referred to the PATHWAYS research team. The research team will then provide study-specific information and invite the family to consider participation in PATHWAYS Trial and/or CONNECT.

No advertisements, public calls, or external referrals will be used. All recruitment will be internal to the NHS CYPGS pathway, ensuring that only those already under specialist care and deemed clinically appropriate are approached. The PATHWAYS research team will not reach out to CYP prior to referral following clinical eligibility assessment. They will not attempt to influence the judgement of the clinical teams or national MDT regarding eligibility or recruitment rates.

PATHWAYS HORIZON Intensive

PATHWAYS researchers will review information provided from PATHWAYS HORIZON participants to identify those who have given assent/consent to be approached for additional research studies. If considered potentially eligible for HORIZON Intensive, based on matching of key characteristics of birth-registered sex, age, presence of not of neurodevelopmental disorders or traits and site, the researcher will contact the CYP's Gender Service to check that they do not want/are not being considered for GnRHa. Following confirmation of this, researchers will reach out directly to CYP and their parent(s)/legal guardian (s) via email to provide information about HORIZON Intensive and CONNECT. This followed up by either an in-person or remote (secure videoconference) meeting to answer any questions. Participants will have the option of assenting/consenting at that visit or delaying a decision as they prefer.

13. Clinical Trials in Emergency Situations

13a. Will the trial recruit participants in an emergency situation whereby consent from the participant cannot be sought or a legal representative cannot be consulted prior to the participant being recruited into the trial?

Yes No

14. Clinical Trials Involving Children

14a. Provide justification for recruiting children

The PATHWAYS Trial, HORIZON Intensive, and CONNECT studies are designed to address a critical gap in the evidence base for the care of children and young people (CYP) with gender incongruence. The study aims to evaluate the potential risks and benefits of pausing puberty for some CYP where this is thought it might be clinically helpful. Puberty can only be paused in adolescence. The inclusion of children under the age of 16 is scientifically and ethically justified based on the following criteria:

1. Importance of the topic: Over the past 10-15 years there has been an exponential rise in the number of CYP seeking care in the NHS because of gender incongruence. The population seeking services differ from earlier patient groups in having greater rates of neurodiversity (autism and ADHD traits and diagnoses) and also a new preponderance of birth-registered females, where birth-registered males previously dominated the patient group. These changes mean that clinical evidence from earlier cohorts is of limited value. Currently, up to 7% of young people describe their gender as 'trans'; despite this high prevalence, we have little knowledge to provide evidence-based care. Hence developing an evidence base is a public health priority.

2. Scientific Grounds for Clinical Equipoise for GnRHa in Treating Gender Incongruence

The available evidence for the benefits versus risks/harms of GnRHa is based on observational studies and does not include the gold standard of randomised controlled trials.

There have been many claims about both benefits (e.g., reduced gender dysphoria, improved quality of life and mental health) and harms (e.g., physical health problems including decreased bone mineral density, possible effects on cognition and learning and increasing the propensity for CYP to retain a trans identity that they might otherwise cast off with typical pubertal development). Neither set of claims is substantiated with high-quality evidence and the silent majority of CYP with gender incongruence and their parents/carers want an evidence base to advise clinical care. Observational studies on their own cannot provide a good evidence base because of the non-randomised allocation of intervention (that means it is not possible to compare those who did and did not receive intervention) and the co-delivery of GnRHa with psychosocial interventions (which means it is not possible to know which intervention(s) had positive effects, if any).

The PATHWAYS Trial is a randomised controlled trial (RCT) evaluating the short- and medium-term benefits and risks/harms of gonadotropin-releasing hormone analogues (GnRHa) for puberty suppression in CYP with gender incongruence. The intervention is already used for this indication in clinical practice in some countries, but its effects have not been rigorously evaluated.

The PATHWAYS trial compares immediate versus delayed initiation of GnRHa, with the aim of determining whether early intervention improves outcomes in domains such as:

Quality of life

Mental health

Gender dysphoria and body satisfaction

Cognitive development

Physical health (e.g. bone mineral density)

The non-randomised comparison arm, HORIZON Intensive, provides an important comparison of matched CYP with gender incongruence receiving psychosocial intervention but not GnRHa,

There are scientific grounds to determine whether receipt of GnRHa might provide direct benefit to the individual CYP, particularly those experiencing high levels of distress related to pubertal development. Previous non-randomised studies have produced inconsistent findings about improvement in mental health and quality of life. The trial includes regular monitoring, psychosocial support, and access to specialist care, which may enhance overall wellbeing regardless of treatment allocation.

3. Scientific Grounds for Population-Level Benefit with Minimal Risk

In addition to potential individual benefit, the trial is expected to generate high-quality evidence that will benefit the broader population of CYP with gender incongruence. This includes:

Clarifying the effects of GnRHa on physical, psychological, and cognitive outcomes

Informing future clinical guidelines and policy decisions

Supporting shared decision-making between CYP, families, and clinicians

The trial is designed to minimise risk and burden. All participants are already under the care of NHS England's specialist gender services and undergo a rigorous clinical eligibility process before being approached for research. The intervention (GnRHa) is administered in line with existing clinical protocols, and participants are closely monitored for adverse effects. The comparator group (delayed start) receives the same level of care and monitoring, ensuring that no participant is denied access to appropriate support.

The main potential harms that have been identified are: negative physical effects of puberty suppression, possible effects on cognition and maintaining CYP that would desist on a trans pathway. In terms of physical effects, including reduction in bone mineral density, there are no longer-term adult data when CYP stop GnRHa. No previous study has examined effects on cognition (nor do they have the data to do this retrospectively). The low rates of desistance/detransitioning do not include systematic follow-up, which has often been less than 50% of the original sample.

4. Ethical Safeguards for Involving Children

The inclusion of children under 16 is ethically justified and supported by robust safeguards:

All participants must be assessed as clinically eligible for GnRHa by both the local clinical team and the national multidisciplinary team (NMDT). This means that the clinical team and national MDT believe that they might benefit from GnRHa.

CYP under 16 must demonstrate Gillick competence, meaning they can understand, retain, and weigh the relevant information and communicate their decision.

A detailed consent and capacity checklist is completed by clinicians over multiple sessions, including one-to-one discussions with the CYP and their parent(s).

At least one person with parental responsibility must also provide consent.

The process is documented in detail, including direct quotes from the CYP and parents to evidence understanding and voluntariness.

These safeguards ensure that participation is based on informed, voluntary decision-making and that the child's best interests are prioritised.

5. Developmental Relevance of the Research

Puberty is a critical developmental period during which gender incongruence may become more pronounced and distressing. The effects of GnRHa are time-sensitive, as they are intended to pause pubertal development. Therefore, it is essential to study the intervention in the age group for whom it is clinically relevant—namely, children in early to mid-puberty (Tanner stages 2–5).

Excluding children from the research would render the findings less applicable to the population most affected by the intervention. It would also perpetuate the current lack of evidence, leaving clinicians and families without the data needed to make informed decisions.

6. Alignment with Regulatory and Ethical Standards

The inclusion of children in the PATHWAYS Trial is consistent with the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the Declaration of Helsinki. The trial has been designed to:

Minimise risk and burden

Maximise potential benefit

Include only those children for whom clinician believe there may be a benefit

Ensure that consent is informed, voluntary, and developmentally appropriate

6. Public and Patient Involvement

The PATHWAYS Engagement Advisory Groups, comprising young people with lived experience, parents, and carers, have been involved in developing the study and the development of participant-facing materials. Their input has ensured that the study is sensitive to the needs and concerns of CYP and their families, and that the language and format of information materials are accessible and inclusive.

Conclusion

The recruitment of children under 16 to the PATHWAYS Trial is scientifically necessary, ethically justified, and supported by comprehensive safeguards. The trial is expected to provide both individual and population-level benefit, with minimal risk and burden. Excluding children from this research would undermine the study's relevance and perpetuate the current evidence gap in the care of CYP with gender incongruence.

14b. How will potential participants be involved in the decision to participate in the trial?

The PATHWAYS Trial has a comprehensive, ethically robust process for involving children and young people (CYP) in the decision to participate, tailored to their developmental stage, cognitive needs, and legal status. The process ensures that participation is informed, voluntary, and appropriately documented.

Involvement of Children and Young People

Children under 16 will be involved in the informed consent process to the fullest extent appropriate for their age and maturity. This includes:

Receiving age-appropriate Participant Information Sheets (PIS), co-developed with young people and parents through the PATHWAYS Engagement Advisory Group.

Reviewing materials in accessible formats, including simplified text, visual aids, and audio recordings of sessions, tailored to individual learning styles and communication needs.

Participating in structured discussions with clinicians and researchers to explore their understanding of the study, including its purpose, procedures, risks, and benefits.

Being encouraged to express their views independently of parental influence, with opportunities for one-to-one discussions with clinicians.

Children will be asked to explain the study in their own words, and a checklist will be used to confirm comprehension of key concepts such as randomisation, fertility implications, and the voluntary nature of participation.

Obtaining and Recording Assent and Consent

Assent will be obtained from CYP under 16 who are deemed Gillick competent. This is assessed through a cumulative clinical process involving multiple sessions with the care team, including paediatric endocrinologists and mental health professionals.

Consent will be obtained from at least one parent or legal guardian. Where possible, both parents will be involved. For TRIAL. The reasons for the absence of one parent will be documented.

For CYP aged 16 and over, informed consent will be obtained directly from the young person, provided they are deemed competent.

All consent and assent will be documented using paper-based forms, signed by the participant and parent/legal guardian, and counter-signed by a medically qualified investigator or delegated sub-investigator.

Who Will Obtain Consent and Their Training

Consent and assent will be obtained by medically qualified investigators or delegated sub-investigators listed on the delegation log. These individuals:

Hold Good Clinical Practice (GCP) certification.

Have experience working with children and young people, particularly those with gender incongruence and neurodevelopmental conditions.

Receive Level 3 safeguarding training.

Are trained in communicating with neurodivergent CYP and those with special communication needs.

Hold NHS contracts, honorary NHS contracts or research passports, ensuring access to NHS support systems and adherence to safeguarding protocols.

Ensuring Understanding and Voluntariness

The consent process is deliberately paced to allow time for reflection and questions. Consent is not obtained at the same time as clinical eligibility is discussed, to avoid any perception of coercion. Participants are reminded that they can withdraw at any time without affecting their clinical care.

The process is subject to oversight by the King's Health Partners Clinical Trials Office to ensure compliance with ethical and legal standards.

14c. How will participants be consented to continue in the trial when they reach the age of legal competence?

The PATHWAYS Trial has clear procedures in place to ensure that participants who reach the age of legal competence (16 years) during the study are re-consented in accordance with ethical and legal standards. At each clinical visit, participants will be routinely asked whether they are happy to continue in the trial or whether they wish to speak to a health-care professional about alternative care. However, all will be formally consented at the first clinical appointment following their 16th birthday.

Identification and Timing

Participants' dates of birth are recorded at enrolment, and the study database is used to monitor when individuals approach their 16th birthday. The research team is alerted in advance to initiate the re-consent process in a timely manner. The research team will then alert a site PI or their designated deputy to undertake the consenting process at the next clinical visit.

Re-Consent Process

Provision of Updated Information

Participants are provided with the most recent version of the Participant Information Sheet (PIS) and consent form, written in age-

appropriate language. These documents explain the study's purpose, procedures, risks, benefits, and the participant's rights, including the right to withdraw at any time.

Consent Discussion

A site PI or their designated deputy per the delegation log with GCP certification and experience working with young people will meet with the participant—either in person or via secure video call—to discuss the study and answer any questions. The discussion ensures that the participant understands the implications of continued participation.

Voluntary Informed Consent

The participant is asked to provide written informed consent to continue in the study. This is done independently of parental involvement unless the participant requests otherwise. The voluntary nature of participation is emphasised.

Documentation

The signed consent form is stored in the Investigator Site File, and a copy is provided to the participant. The re-consent is also recorded in the study database.

Ongoing Support

If there are concerns about the participant's capacity to consent, additional support and time are provided. The process is paused until the participant is ready to make an informed decision.

15. Impartial Witness

15a. Is the trial likely to include participants who are unable to sign the consent form and therefore an impartial witness would be required?

Yes No

16. Cluster Trials

16a. Will the trial involve the recruitment and allocation of an IMP to groups of participants rather than individual participants (cluster trial)?

Yes No

I. Payment of Compensation

1. Will payment or compensation be offered?

Yes No

1a. Who will payment or compensation be offered to?

- Participants
- Parent/carer
- Legal representatives
- Other

1b. What will be the format of the payment or compensation?

- Travel expenses
- Accommodation expenses
- Meal expenses
- Loss of earnings
- Monetary payment
- Non-monetary payment
- Other

1b.1. State how much?

Participants time for completing annual questionnaires will be acknowledged with a voucher worth £20.

2. Describe arrangements for how any payment or compensation will be paid/provided

Any travel, accommodation and subsistence costs incurred by travelling to London for PATHWAYS CONNECT fMRI/sMRI will be reimbursed by bank transfer. £20 vouchers for completing annual questionnaires will be based on participant preference e.g. amazon vouchers.

3. Are there any conditions attached to the payment or compensation?

Yes No

3a. If yes, please specify

For the £20 vouchers, participants must have completed annual questionnaires hosted on the Medrio e-Patient Reported Outcomes (ePRO) module.

A. Trial Identification

A3. Full title of the trial

Please note details entered here will be inserted into Study Information A6

Puberty Suppression and Transitional Healthcare with Adaptive Youth Services (PATHWAYS). PATHWAYS TRIAL, PATHWAYS CONNECT, and PATHWAYS HORIZON Intensive.

A3-2. Name or abbreviated title of the trial where available

Please return to [Update project details](#) if you need to amend the short project title entered here.

PATHWAYS TRIAL

A4-1. Sponsor's protocol code number:

3646-PATHWAYS

A4-2. Sponsor's protocol version:

1.0

A4-3. Sponsor's protocol date:

20 August, 2025

A5-1. ISRCTN number

—

A5-2. ClinicalTrials.gov number

—

A5-3. WHO Universal Trial Reference Number (UTRN)

—

A5-4. Other Identifiers:

| Name | Identifier |
|----------|------------|
| No items | |

B. Identification of the sponsor responsible for the request

B1-1 Name of organisation

King's College London

B1-2 Name of person to contact:

B1-2-1 Given Name

██████

B1-2-2 Middle Name

B1-2-3 Family Name

██████

Address

Street Address

KHP-CTO, Floor 16 Tower Wing, Guy's Hospital, Great Maze Pond

Town/City

London

Post Code

SE1 9RT

Country

United Kingdom

Telephone Number

Country Dialing Prefix

+44

Local Area Code

020

Phone Number

██████████

Extension

n/a

Fax Number

Country Dialing Prefix

Extension

Local Area Code

Phone Number

E-mail

QM.KHPCTO@kcl.ac.uk

B1-1 Name of organisation

South London and Maudsley NHS Foundation Trust

B1-2 Name of person to contact:

B1-2-1 Given Name

██████

B1-2-2 Middle Name

B1-2-3 Family Name

██████

Address

Street Address

R&D, W1.08, IOPPN, 16 De Crespigny Park

Town/City

London

Post Code

SE5 8AF

Country

United Kingdom

Telephone Number

| Country Dialing Prefix | Local Area Code | Phone Number | Extension |
|------------------------|-----------------|--------------|-----------|
| +44 | 020 | ■ | ■ |

Fax Number

| Country Dialing Prefix | Local Area Code | Phone Number |
|------------------------|-----------------|--------------|
| | | |

Extension

E-mail

slam-ioppn.research@kcl.ac.uk

E. General Information on the Trial

E2. Objective of the trial

E2-1. Main objective of the trial

To establish the potential short to medium term benefits and risks of using gonadotropin-releasing hormone analogues (GnRHa - also known as puberty suppressing hormones) in children and young people (CYP) with gender incongruence. This will look at a wide range of possible benefits and risks, including how the treatment affects quality of life, mental health, gender identity, satisfaction with one's body, thinking and brain development, and physical health like bone strength.

E2-2. Secondary objectives of the trial

1. Find out which outcomes are most important to CYP who are taking GnRHa, such as feeling better in their own body, improving mental health, or doing better in every day life.
2. To better understand the young people seeking treatment of gender incongruence with GnRHa and evaluate key areas of their lives, including:
 - Social and emotional function
 - Mental health
 - Feelings about their gender and body
 - Physical health and growth
 - Development of their thinking and brain
 - Side effects or safety concerns
 - Thoughts about preserving fertility
 - Effect(s) of mental health or neurodevelopmental conditions
 - Effects of family, school and social environments
3. Explore decisions CYP make at the end of treatment with GnRHa, whether they continue, start cross-sex hormone treatment, or stopping/pausing hormone-related treatment.
4. To follow up participants long-term, to learn how choices and experiences shape well-being, identity, and health as they develop

E7. Trial type and phase

E7-1. Human pharmacology (Phase I)

Yes No Not Answered

E7-2. Therapeutic exploratory (Phase II)

Yes No Not Answered

E7-3. Therapeutic confirmatory (Phase III)

Yes No Not Answered

E7-4. Therapeutic use (Phase IV)

Yes No Not Answered

E8-9. Initial estimate of the duration of the trial (years, months, days)

E8-9-1. In the MS concerned

Years

5

Months

6

Days

0

F. Population Of Trial Subjects

F1. Age Range

F1-1. Are the trial subjects under 18?

Yes No Not Answered

F1-2. Number of subjects for this age range:

526

F1-1-1. In utero

Yes No Not Answered

F1-1-2. Preterm newborn infants (up to gestational age less than 37 weeks)

Yes No Not Answered

F1-1-3. Newborn (0-27 days)

Yes No Not Answered

F1-1-4. Infant and toddler (28 days - 23 months)

Yes No Not Answered

F1-1-5. Children (2-11 years)

Yes No Not Answered

F1-1-6. Adolescent (12-17 years)

Yes No Not Answered

F1-1-6-1. Number of subjects for this age range:

526

F1-2. Adult (18-64 years)

Yes No Not Answered

F1-3. Elderly (greater than 65 years)

Yes No Not Answered

F2. Gender

F2-1. Female

Yes No Not Answered

F2-2. Male

Yes No Not Answered

F3. Group of trial subjects

F3-1. Healthy volunteers

Yes No Not Answered

F3-2. Patients

Yes No Not Answered

F3-3. Specific vulnerable populations

Yes No Not Answered

F3-3-1. Women of childbearing potential not using contraception

Yes No Not Answered

F3-3-2. Women of childbearing potential using contraception

Yes No Not Answered

F3-3-3. Pregnant women

Yes No Not Answered

F3-3-4. Nursing women

Yes No Not Answered

F3-3-5. Emergency situations

Yes No Not Answered

F3-3-6. Subjects incapable of giving consent personally

Yes No Not Answered

F3-3-6-1. If yes, please specify:

Participants who are children (under 16 years of age)

F3-3-7. Others

Yes No Not Answered

F4. Planned number of subjects to be included

F4-1. In the member state

526

F5. Plans for treatment or care after a subject has ended his/her participation in the trial.

If it is different from the expected normal treatment, please specify:

At the primary endpoint, CYP will have a comprehensive review involving discussion between them, their parent(s)/caregiver(s), and the paediatric endocrinologist in charge of their care. It will be recorded whether the onward treatment plan is to include continued intervention with GnRHa, move to initiation of cross-sex hormones, pause/stopping GnRHa or another choice (to be specified). If there is full agreement between the 3 parties, the clinician will present the case to the national MDT.

G. Investigator Details

G1. National coordinating investigator (for a multicentre trial) or principal investigator (for a single centre trial)

National Coordinating Investigator

G1-1. Given Name

████

G1-2. Middle Name

G1-3. Family Name

████

G1-4. Qualification (MD...)

BA, MD, FRCPsych

G1-5. Institution Name

Kings College London

G1-5. Institution Department Name

Child and Adolescent Psychiatry

Address

Street Address

Department of Child and Adolescent Psychiatry, IOPPN, 16 De Crespigny Park

Town/City

London

Post Code

SE5 8AF

Country

United Kingdom

G1-5-5. Please indicate if site is:

Non-NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

020

Phone Number

████

Extension

████

Fax Number

Country Dialing Prefix

Extension

Local Area Code

Phone Number

E-mail

████@kcl.ac.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

████

G2-2. Middle Name

G2-3. Family Name

████

G2-4. Qualification (MD...)

BSc, MBBS, MRCPCH, PhD

G2-5. Institution Name

University College London Hospitals NHS Foundation Trust

G2-5. Institution Department Name

Paediatric Endocrinology

Address

Street Address

University College London Hospital, 235 Euston Road

Town/City

London

Post Code

NW1 2BU

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

| Country Dialing Prefix | Local Area Code | Phone Number | Extension |
|------------------------|-----------------|--------------|-----------|
| +44 | 020 | ██████████ | n/a |

Fax Number

| Country Dialing Prefix | Local Area Code | Phone Number |
|------------------------|-----------------|--------------|
| | | |

Extension

E-mail

██████████@nhs.net

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

██████████

G2-2. Middle Name

G2-3. Family Name

██████████

G2-4. Qualification (MD...)

BSc, MB, BS, FRCPCH, PhD

G2-5. Institution Name

University Hospitals Bristol NHS
Foundation Trust

G2-5. Institution Department Name

Paediatric Endocrinology

Address

Street Address

Bristol Royal Hospital For Children, Upper Maudlin Street

Town/City

Bristol

Post Code

BS2 8BJ

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

| Country Dialing Prefix | Local Area Code | Phone Number | Extension |
|------------------------|-----------------|--------------|-----------|
| +44 | ██████████ | ██████████ | n/a |

Fax Number

| Country Dialing Prefix | Local Area Code | Phone Number |
|------------------------|-----------------|--------------|
| | | |

Extension

E-mail

██████████@uhbw.nhs.uk

G2. What is the role of this investigator?

G2 Other principal investigator for a multicentre trial

G2-1. Given Name

██████████

G2-2. Middle Name

G2-3. Family Name

██████████

G2-4. Qualification (MD...)

PhD, FRCPCH

G2-5. Institution Name

Great Ormond Street Hospital for Children
NHS Foundation Trust

G2-5. Institution Department Name

Gender Service

Address

Street Address

Great Ormond Street Hospital, Great Ormond Street

Town/City

London

Post Code

WC1N 3JH

Country

United Kingdom

G2-5-5. Please indicate if site is:

NHS

Telephone Number

Country Dialing Prefix

+44

Local Area Code

020

Phone Number

██████████

Extension

n/a

Fax Number

Country Dialing Prefix

Extension

Local Area Code

Phone Number

E-mail

██████████@kcl.ac.uk