# Puberty Suppression and Transitional Healthcare with Adaptive Youth Services (PATHWAYS):

## PATHWAYS TRIAL, PATHWAYS CONNECT and PATHWAYS HORIZON-INTENSIVE

### Trial Identifiers

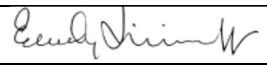
| | | | |
|---|---|---|---|
| **IRAS:** | 1011645 | | |
| **ISRCTN:** | TBC | | |
| **Funder Number:** | NIHR167530 | | |
| **Protocol Version Number:** | 2.2 | **Date:** | 20.11.2025 |

### Co-Sponsors

| | |
|---|---|
| **Name:** | King's College London |
| **Email:** | Ann-Marie Murtagh, QM.KHPCTO@kcl.ac.uk |

| | |
|---|---|
| **Name:** | South London and Maudsley NHS Foundation Trust |
| **Email:** | slam-ioppn.research@kcl.ac.uk |

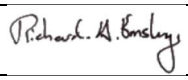
### Chief Investigator

| | | |
|---|---|---|
| **Name:** | Professor Emily Simonoff | |
| **Signature** |  | 20/11/2025 |

### Joint Co-Lead

| | | |
|---|---|---|
| **Name:** | Dr Michael Absoud | |
| **Signature** | Michael Absoud (20/11/2025 13:04:45 GMT) | 20/11/2025 |

### Methodologist

| | | |
|---|---|---|
| **Name:** | Professor Richard Emsley | |
| **Signature** |  | 20/11/2015 |

### Clinical Trials Unit

| | |
|---|---|
| **Name:** | King's Clinical Trials Unit |
| **Email:** | PATHWAYSstudy@kcl.ac.uk |

## Study Synopsis

| | |
|---|---|
| **Title Of Clinical Trial:** | Puberty Suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS): PATHWAYS TRIAL |
| **Protocol Short Title/ Acronym:** | PATHWAYS TRIAL |
| **Study Phase:** | 3 |
| **Sponsor Name(s):** | King's College London<br>South London and Maudsley NHS Foundation Trust |
| **Chief Investigator(s):** | Professor Emily Simonoff<br>Dr Michael Absoud (Deputy CI) |
| **Medical Condition or Disease Under Investigation:** | Gender Incongruence |
| **Purpose of Clinical Trial:** | To evaluate benefits and risks of using gonadotropin-releasing hormone analogues (GnRHa) for puberty suppression in children and young people (CYP) with gender incongruence. |
| **Primary Objective:** | To determine the short/medium-term benefits and risks of GnRHa for puberty suppression in CYP with gender incongruence. This will take a comprehensive approach to domains of possible benefit and risk, including quality of life, mental health, gender identity/dysphoria and body satisfaction, impact on cognition and brain development and physical effects including bone mineral density. |
| **Secondary Objective(s):** | To understand which potential outcomes (e.g., domains of quality of life, mental health, gender and body distress, cognition, physical health) are the priority goals for CYP receiving GnRHa.<br>To allow for future safety, efficacy, and effectiveness data, including rarer adverse effects and long-term effects, pending further funding. |
| **Exploratory Objectives** | 1. Do short-term/risk benefit profiles vary according to Tanner stage?<br>2. Do risk benefit profiles vary according to birth-registered sex?<br>3. Do risk benefit profiles vary according to presence or not of neurodevelopmental disorders or high levels of neurodevelopmental trait levels?<br>4. Do risk benefit profiles vary according to length of GnRHa treatment? |
| **Primary Outcome Measure** | KIDSCREEN-10 health-related quality of life questionnaire |
| **Secondary Outcome Measures** | Scales of Gender-Related Distress, Mental Health Symptoms and Physical Health measures :<br>a) Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS) |

b) Revised Children's Anxiety and Depression Scale (RCADS)
c) Body Image Scale – Gender Spectrum (BIS-GS)
d) Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y)
e) SCOFF questionnaire
f) Sexual attraction questionnaire
g) ALSPAC measure
h) Gender identity question
i) Adolescent Primary Care Traumatic Stress Screen (APCTSS)
j) KIDSCREEN-52
k) Height (cm) and weight (kg)
l) Physical health diagnoses

Scales of Suicidal Ideation, Hospitalizations, Mood Symptoms, Behavioural and Functional Difficulties:

a) Ask Suicide-screening Questions (ASQ)
b) Child Behaviour Checklist (CBCL)
c) Youth Self-Report (YSR)
d) Difficulties in Emotion Regulation Scale – 18 (DERS-18)
e) Hospitalisations of participants

Experiences of Therapeutic Options:

a) Rates of referral to, uptake of, and completion of psychological therapy, occupational therapy, speech and language therapy, clinical nursing, youth work support, school/college support, and non-endocrine pharmacological treatments.

Cognitive Assessments

a) Wechsler Intelligence Scale for Children (WISC-V)
b) Delis-Kaplan Executive Function System (D-KEFS)
c) Child and Adolescent Memory Profile (CHAMP)
d) Memory Validity Profile (MVP)
e) Behaviour Rating Inventory of Executive Function (BRIEF)

Continuous Physical Measures

a) Height (cm)
b) Weight (kg)
c) BMI
d) Bone mineral density (DEXA) z score
e) Blood pressure; systolic, diastolic, mean

| | |
|---|---|
| | f) Safety bloods<br><br>Binary Physical Outcomes<br>a) Adverse events<br>b) Puberty staging (Tanner staging, both clinical and self-reported) |
| **Trial Design:** | Randomised Controlled Trial (RCT) comparing immediate vs. delayed start (1 year post-randomisation) of GnRHa amongst 226 CYP with primary endpoint at 2 years post-randomisation. Midpoint comparisons determine short-term differences due to receipt of GnRHa while endpoint comparisons determine whether the groups converge or GnRHa timing/duration influences outcome. A non-randomised control group (HORIZON INTENSIVE) will include a matched group of CYP not receiving GnRHa. |
| **Sample Size:** | 226 participants |
| **Summary of Clinical Eligibility Criteria:** | <u>Inclusion criteria:</u><br>1. Diagnosis of gender incongruence according to ICD-11, which includes:<br>a. Strong desire to be a different gender than the birth-assigned sex.<br>b. Strong dislike of sexual anatomy or anticipated secondary sex characteristics.<br>c. Gender Incongruence persisted for a minimum of 2 years.<br>d. Strong desire to 'transition' and live as the experienced gender.<br>2. Request for puberty suppression persists after receiving other care prior to the initiation of GnRHa.<br>3. Confirmed Tanner stage 2-5.<br>4. Younger than 15 years and 11 months at the time of consent.<br>5. Leading clinician considers there is a reasonable prospect of benefit from GnRHa for puberty suppression.<br>6. Leading clinician believes they have participated sufficiently for their holistic health in other forms of care for puberty suppression to be considered, in line with national MDT recommendations and this participation is reviewed by the national MDT.<br>7. Sufficient understanding of treatment advantages and disadvantages on part of the CYP; Fertility preservation discussed. |

| | |
|---|---|
| | 8. At least one parent or legal guardian has demonstrated sufficient understanding of the possible advantages and disadvantages of treatment; demonstrated they can retain key information to provide informed consent<br>9. The CYP and parent(s)/legal guardian(s) are willing to be randomised into either study arm, documented by signed informed consent (parent/guardian) and assent (CYP).<br><br><u>Exclusion criteria:</u><br>1. Physical conditions preventing puberty commencement or advancement.<br>2. Unstable physical health requiring active intervention.<br>3. Hypersensitivity to GnRH, its analogues, or any of its excipients.<br>4. Known congenital long QT syndrome<br>5. Unstable mental health impairing ability to provide informed assent/consent.<br>6. Family/home situation affecting adherence to protocol.<br>7. Clinical concerns about capacity to consent.<br>8. Insufficient understanding of PATHWAYS TRIAL<br>9. New or ongoing safeguarding concerns.<br>10. Birth-registered females with undiagnosed vaginal bleeding.<br>11. Birth-registered females who are pregnant or lactating<br>12. Individuals of child-bearing potential who are at risk of pregnancy during the trial |
| **Summary of research eligibility criteria** | <u>Inclusion criteria</u><br>1. Clinician in CYPGS believes GnRHa treatment for 2 or more years may be helpful to the CYP. No current plan to initiate cross-sex hormone treatment in the next two years.<br>2. Written informed assent and consent from CYP and parent/legal guardian respectively.<br>3. The CYP and their parent have reviewed the suite of measures, including physical health investigations, cognitive assessments and questionnaires, and understand that their completion is required for the clinical trial.<br>4. Participants who are sexually active agree to use contraception throughout the trial. |

| | |
|---|---|
| | Exclusion criteria<br>1. The CYP has previously taken or is currently using GnRHa for this indication<br>2. The CYP is or has taken cross-sex hormones for gender incongruence/dysphoria<br>3. Participant is involved in another research trial |
| **Intervention (Description, frequency, details of delivery)** | Decapeptyl® SR (long-acting formulation of Triptorelin) 22.5mg injections.<br><br>Administration: Intramuscular injections every six months at 0, 6, 12, 18 and 24 months post-randomisation. Option to move to 3-monthly or 1-monthly injections based on clinical grounds.<br><br>Monitoring: Regular follow-up appointments to assess efficacy and safety, including monitoring hormone levels and physical development. Routine blood tests, DEXA scans, and physical assessments (height, weight, BMI, blood pressure, and puberty staging). Psychosocial screening to identify any unmet needs and escalate these to appropriate services. |
| **Comparator Intervention:** | Delayed Start: Participants in the delayed start group will be offered GnRHa treatment one year after randomisation. They will receive the same monitoring and assessments as the immediate start group. |
| **Maximum Duration of Treatment of a Participant:** | 24 months in randomised trial with potential for non-randomised open extension according to clinical compassionate care. |

**Study Synopsis**

| | |
|---|---|
| **Title Of Clinical Trial:** | Puberty Suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS): PATHWAYS HORIZON INTENSIVE |
| **Protocol Short Title/ Acronym:** | PATHWAYS HORIZON INTENSIVE |
| **Study Phase:** | Observational |
| **Sponsor Name(s):** | King's College London<br>South London and Maudsley NHS Foundation Trust |
| **Chief Investigator(s):** | Professor Emily Simonoff<br>Dr Michael Absoud (Deputy CI) |
| **Medical Condition or Disease Under Investigation:** | Gender Incongruence |
| **Purpose of Study:** | To provide a non-randomised control group of CYP with gender incongruence not receiving GnRHa who will be compared to TRIAL participants with respect to outcomes. |

| | |
|---|---|
| **Primary Objective:** | To provide a naturalistic comparison to participants in TRIAL with respect to benefits and risks of GnRHa over 24 months. Participants will be assessed with the same measures of possible benefit and harms as for TRIAL. |
| **Secondary Objective(s):** | To compare the priority goals of CYP with gender incongruence not receiving GnRHa to those in TRIAL<br>To track the trajectories of cognition in CYP who are not receiving GnRHa |
| **Primary Outcome Measure** | KIDSCREEN-10 health-related quality of life questionnaire |
| **Secondary Outcome Measures** | Scales of Gender-Related Distress, Mental Health Symptoms and Physical Health measures :<br>a) Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS)<br>b) Revised Children's Anxiety and Depression Scale (RCADS)<br>c) Body Image Scale – Gender Spectrum (BIS-GS)<br>d) Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y)<br>e) SCOFF questionnaire<br>f) Sexual attraction questionnaire<br>g) ALSPAC measure<br>h) Gender identity question<br>i) Adolescent Primary Care Traumatic Stress Screen (APCTSS)<br>j) KIDSCREEN-52<br>k) Height (cm) and weight (kg)<br>l) Physical health diagnoses<br><br>Scales of Suicidal Ideation, Hospitalizations, Mood Symptoms, Behavioural and Functional Difficulties:<br>a) Ask Suicide-screening Questions (ASQ)<br>b) Child Behaviour Checklist (CBCL)<br>c) Youth Self-Report (YSR)<br>d) Difficulties in Emotion Regulation Scale – 18 (DERS-18)<br>e) Hospitalisations of participants<br><br>Experiences of Therapeutic Options:<br>a) Rates of referral to, uptake of, and completion of psychological therapy, occupational therapy, speech and language therapy, clinical nursing, youth work support, school/college support, and non-endocrine pharmacological treatments. |

| | |
|---|---|
| | Cognitive Assessments<br>a) Wechsler Intelligence Scale for Children (WISC-V)<br>b) Delis-Kaplan Executive Function System (D-KEFS)<br>c) Child and Adolescent Memory Profile (CHAMP)<br>d) Memory Validity Profile (MVP)<br>e) Behaviour Rating Inventory of Executive Function (BRIEF)<br><br>Continuous Physical Measures<br>a) Height (cm)<br>b) Weight (kg)<br>c) BMI<br>d) Bone mineral density (DEXA) z score<br>e) Blood pressure; systolic, diastolic, mean<br>f) Safety bloods<br><br>Binary Physical Outcomes<br>a) Adverse events<br>b) Puberty staging (self-reported) |
| **Trial Design:** | Observation of non-randomised control group |
| **Sample Size:** | 300 participants. Participants will be balanced with respect to stratifiers for TRIAL: site, age (as indicative of likely pubertal stage), presence of neurodevelopmental disorders or high trait levels and birth-registered sex. |
| **Summary of Eligibility Criteria:** | <u>Inclusion Criteria</u><br>1. Participating in the PATHWAYS HORIZON study<br>2. Has agreed to be contacted for other research studies<br><br><u>Exclusion Criteria</u><br>1. Is considered clinically eligible for GnRHa and wishes to receive this intervention<br>2. A decision regarding clinical eligibility for GnRHa is pending<br>3. CYP has previously used GnRHa or gender-affirming hormones for gender incongruence |

**Study Synopsis**

| | |
|---|---|
| **Title Of Clinical Trial:** | Puberty Suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS): PATHWAYS CONNECT |
| **Protocol Short Title/ Acronym:** | PATHWAYS CONNECT |
| **Study Phase:** | Observational |
| **Sponsor Name(s):** | King's College London<br>South London and Maudsley NHS Foundation Trust |
| **Chief Investigator(s):** | Professor Emily Simonoff<br>Dr Michael Absoud (Deputy CI) |
| **Medical Condition or Disease Under Investigation:** | Gender Incongruence |
| **Purpose of Clinical Trial:** | To determine whether GnRHa during puberty in CYP with gender incongruence affects brain development. |
| **Primary Objective:** | To map trajectories of brain development in CYP with gender incongruence, comparing those receiving GnRHa immediately (two years) vs delayed start (one year) with a non-randomised comparison group from HORIZON INTENSIVE not receiving GnRHa |
| **Secondary Objective(s):** | To link trajectories of brain development to cognitive measures, including general intelligence, memory and executive function. |
| **Trial Design:** | Longitudinal observational study comparing participants from TRIAL and HORIZON INTENSIVE. |
| **Sample Size:** | 250 participants (150 from TRIAL, 100 from HORIZON INTENSIVE). |
| **Summary of Eligibility Criteria:** | <u>Inclusion Criteria</u><br>1. Participant is a member of PATHWAYS TRIAL or PATHWAYS HORIZON INTENSIVE.<br>2. Participant is willing to participate in brain imaging study, including travelling to London (King's College London).<br>3. Participant provides informed assent (for u16) or consent (for 16+).<br>4. Parent/legal guardian provides consent.<br><u>Exclusion Criteria</u><br>1. MR imaging is contra-indicated (e.g. ferro-magnetic metal implants). |

**Revision History**

| Protocol version | Description of changes from previous revision | Effective Date |
|---|---|---|
| Protocol Version 2.0 | Approved Protocol | 29.09.25 |
| Protocol Version 2.1 | Pre-approval revision history removed | 20.11.25 |
| Protocol Version 2.2 | Funder logo removed | 20.11.25 |

**Glossary of terms**

| | | | | |
|---|---|---|---|---|
| **AE/AR** | Adverse Event/Adverse Reaction | | **MRI** | Magnetic Resonance Imaging |
| **CA** | Competent Authority | | **MTA** | Material Transfer Agreement |
| **CI** | Chief Investigator | | **NMDT** | National Multidisciplinary Review Team |
| **CNS** | Clinical Nurse Specialist | | **NIHR** | National Institute for Health and Care Research |
| **CONSORT** | Consolidated Standards of Reporting Trials | | **NRCP** | National Research Collaboration Programme |
| **CRF** | Case Report Form | | **PI** | Principal Investigator (at site) |
| **CSV** | Comma-Separated Values | | **PIN** | Participant Identification Number |
| **CTIMP** | Clinical Trial of Investigational Medicinal Product | | **PIS** | Participant Information Sheet |
| **CTU** | Clinical Trials Unit | | **PMG** | Programme Management Group |
| **CYP** | Children and Young People | | **PP** | Per Protocol |
| **CYPGS** | Children and Young Person's Gender Service (CYPGS) | | **PSC** | Programme Steering Committee |
| **DCR** | Data Clarification Request | | **R&D** | Research and Development |
| **DEXA** | Dual X-Ray Absorptiometry | | **RA** | Regulatory Agency |
| **DMC** | Data Monitoring Committee | | **RCT** | Randomised Controlled Trial |
| **DSUR** | Development Safety Update Report | | **REC** | Research Ethics Committee |
| **eCRF** | Electronic Case Report Form | | **RN** | Research Nurse |
| **EDC** | Electronic Data Capture | | **RSI** | Reference Safety Information |
| **ePRO** | Electronic Participant Reported Outcome | | **SAE** | Serious Adverse Event |
| **GP** | General Practitioner | | **SAP** | Statistical Analysis Plan |
| **GCP** | Good Clinical Practice | | **SOP** | Standard Operating Procedure |
| **GnRHa** | Gonadotropin Releasing Hormone Analogues | | **SAR** | Serious Adverse Reaction |
| **HRA** | Health Research Authority | | **SDV** | Source Data Verification |
| **ICF** | Informed Consent Form | | **SmPC** | Summary of Product Characteristics |
| **ID** | Identifier | | **SS** | Senior Statistician |
| **IME** | Important Medical Events | | **SDW** | Source Data Worksheets |
| **IMP** | Investigational Medicinal Product | | **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **IMPD** | Investigational Medicinal Product Dossier | | **TM** | Trial Manager |
| **ITT** | Intention to Treat | | **TS** | Trial Statistician |
| **KCTU** | King's Clinical Trials Unit | | **UK** | United Kingdom |
| **KHP-CTO** | King's Health Partners Clinical Trials Office | | **UAR** | Unexpected Adverse Reaction |
| **MHRA** | Medicines and Healthcare products Regulatory Agency | | **VR** | Virtual Reality |

# Table of Contents

**1 Introduction ..... 20**
1.1 Studies included in this protocol ..... 20
1.2 Background and rationale ..... 20
1.2.1 Epidemiology and presentation to services ..... 20
1.2.2 Puberty suppression and changes in care ..... 21
1.3 Summary of PATHWAYS Research Programme ..... 22
1.3.1 PATHWAYS HORIZON ..... 23
1.3.2 HORIZON INTENSIVE ..... 23
1.3.3 PATHWAYS TRIAL ..... 23
1.3.4 PATHWAYS CONNECT ..... 23
1.3.5 PATHWAYS VOICES ..... 24
1.3.6 PATHWAYS ENGAGEMENT ..... 24
1.4 Relationship between PATHWAYS studies ..... 24
1.5 Rationale for a Randomised Controlled Trial ..... 25
1.5.1 Clinical equipoise ..... 25
1.5.2 Retrospective studies. ..... 26
1.5.3 Must the research be undertaken with children and young people, who are a vulnerable population? ..... 26
1.5.4 Long-term benefits ..... 26
**2 Trial Design ..... 27**
2.1 Rationale for Trial Design ..... 28
2.1.1 Why not use a placebo-controlled, double-blind design? ..... 28
2.2 Choice of immediate vs delayed treatment arms. ..... 28
2.3 Intervention Delivery and Monitoring ..... 30
2.4 Objectives ..... 30
2.4.1 Primary Objective ..... 30
2.4.2 Secondary Objectives ..... 31
2.4.3 Exploratory Objectives ..... 31
**3 Participants ..... 32**
3.1 Study setting & recruitment ..... 32
3.2 Eligibility criteria for TRIAL ..... 32
3.2.1 Clinical eligibility for GnRHa ..... 32
**3.2.1.1.1 CYPGS NMDT ..... 32**

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

3.2.1.2 Clinical Inclusion Criteria ..... 33
3.2.1.3 Clinical Exclusion Criteria ..... 34
3.2.1.4 Research Inclusion Criteria ..... 36
3.2.1.5 Research Exclusion Criteria ..... 36
3.3 Eligibility Criteria for HORIZON INTENSIVE ..... 37
3.3.1 HORIZON INTENSIVE Inclusion Criteria ..... 37
3.3.2 HORIZON INTENSIVE Exclusion Criteria ..... 37
3.4 Eligibility Criteria for PATHWAYS CONNECT ..... 37
3.4.1 PATHWAYS CONNECT Inclusion Criteria ..... 37
3.4.2 PATHWAYS CONNECT Exclusion Criteria ..... 38
3.5 Informed Consent ..... 38
3.5.1 Informed Consent for TRIAL ..... 38
3.5.1.1 The process of determining clinical eligibility ..... 38
3.5.1.2 The process of informed consent to participate in TRIAL ..... 40
3.5.2 Informed Consent for HORIZON INTENSIVE ..... 41
3.5.3 Informed Consent for CONNECT ..... 41
**4 Data Collection & Data Entry ..... 42**
4.1 Participant Timeline ..... 42
4.2 Visit Windows ..... 46
4.2.1 TRIAL ..... 46
4.2.2 HORIZON INTENSIVE ..... 46
4.2.3 CONNECT ..... 46
4.3 Screening Visit ..... 46
4.4 Baseline Visit ..... 47
4.5 Month 3, 6, 9, 12, 15, 18, 21 visits ..... 47
4.6 Month 24 or end-of-study visit ..... 47
4.7 Continuing care ..... 47
4.8 Withdrawal visit ..... 48
4.9 Data Entry ..... 48
4.10 Pre-randomisation data collection ..... 49
4.10.1 Registration ..... 49
4.10.2 Eligibility ..... 49
4.10.3 Medical History ..... 49

4.10.4 Demographics ..... 50
4.10.5 Randomisation ..... 50
4.11 Baseline characteristics ..... 50
4.11.1 Swanson, Nolan, and Pelham-IV (SNAP-IV) ..... 50
4.11.2 'About Yourself' Questionnaire for Parents/Caregivers ..... 50
4.11.3 Social Communication Questionnaire (SCQ) ..... 50
4.12 Efficacy data ..... 51
4.12.1 PRIMARY OUTCOME - KIDSCREEN-10 ..... 51
4.12.2 Secondary Outcomes ..... 51
4.12.2.1 KIDSCREEN-52 ..... 51
4.12.2.2 Gender Identity ..... 51
4.12.2.3 Social Transition Questionnaire ..... 52
4.12.2.4 Personal Priorities ..... 52
4.12.2.5 Adolescent Primary Care Traumatic Stress Scale (APCTSS) ..... 52
4.12.2.6 Revised Child Anxiety and Depression Scale (RCADS) ..... 52
4.12.2.7 Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) ..... 52
4.12.2.8 Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS) ... 53
4.12.2.9 Body Image Scale – Gender Spectrum (BIS-GS) ..... 53
4.12.2.10 Ask Suicide-Screening Questions (ASQ) ..... 53
4.12.2.11 SCOFF Questionnaire ..... 53
4.12.2.12 Difficulties in Emotion Regulation Scale (DERS) ..... 54
4.12.2.13 Sexual Attraction ..... 54
4.12.2.14 Romantic Relations ..... 54
4.12.2.15 Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES) 54
4.13 Cognitive Assessments ..... 55
4.13.1 Wechsler Intelligence Scale for Children (WISC-V) ..... 55
4.13.2 Delis-Kaplan Executive Function System (D-KEFS) ..... 55
4.13.3 Child and Adolescent Memory Profile (CHAMP) ..... 55
4.13.4 Memory Validity Profile (MVP) ..... 55
4.13.5 Behaviour Rating Inventory of Executive Function (BRIEF) ..... 55
4.14 Safety Data ..... 56
4.14.1 Physical Exam ..... 56

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

4.14.2 Electrocardiogram (ECG) ..... 56
4.14.3 Puberty Staging Assessment (Tanner staging) – Clinical Examination..... 56
4.14.4 Puberty Staging Assessment – Self-Reported..... 57
4.14.5 Vital Signs..... 57
4.14.6 Dual X-Ray Absorptiometry (DEXA) Scan ..... 57
4.14.7 Bone Age X-Ray ..... 57
4.14.8 Adverse Events..... 58
4.14.9 Concomitant Medications..... 58
4.14.10 Withdrawal ..... 58
4.15 Laboratory Data ..... 59
4.15.1 Safety Bloods..... 59
4.15.1.1 TRIAL Participants ..... 59
4.15.1.2 HORIZON INTENSIVE Participants ..... 60
4.15.2 Pregnancy Tests ..... 61
4.15.3 Urinalysis ..... 61
4.16 Injection Visit Safety Data Collection ..... 61
4.17 Magnetic Resonance Imaging Data..... 62
4.17.1 MRI Imaging Protocol..... 62
4.17.1.1 Incidental Findings ..... 63
4.18 IMP Dosing Data..... 63
4.18.1 Study Medication Dispensing and Dosing Log..... 63
4.19 Measures to promote participant retention ..... 63
**5 Interventions..... 63**
5.1 Explanation for the choice of comparators ..... 63
5.2 Intervention and comparator description, dosing and labelling and intervention..... 64
5.2.1 Medication:..... 64
5.2.2 Labelling:..... 64
5.2.3 Administration: ..... 64
5.2.4 Monitoring: ..... 64
5.2.5 Fertility Preservation:..... 65
5.2.6 Comparator: ..... 65
5.3 IMP accountability ..... 65
5.4 IMP Storage ..... 65

5.5 Returns & Destruction ..... 65
5.6 Discontinuing allocated interventions ..... 65
5.7 Concomitant medications permitted or prohibited during the trial ..... 66
5.7.1 Permitted Medications ..... 66
5.7.2 Prohibited medications ..... 66
5.7.3 Non-prohibited Concomitant Potentially QT-Prolonging Drug Risk Management Algorithm ..... 66
**6 Assignment of Interventions ..... 68**
6.1 Randomisation method ..... 68
6.2 Randomisation implementation ..... 68
Allocation sequence generation ..... 68
Enrolment of participants ..... 68
Assignment of participants to interventions ..... 68
Randomisation procedure ..... 68
6.3 Blinding status of researchers ..... 68
**7 Data Management ..... 69**
7.1 Data Handling and Management ..... 69
7.1.1 Medrio EDC ..... 70
7.1.1.1 Medrio ePRO ..... 70
7.1.2 KCTU Randomisation System ..... 71
7.1.3 Q-Interactive ..... 72
7.2 Data security ..... 72
7.2.1 Medrio and KCTU Randomisation System ..... 72
7.2.2 Q-Interactive ..... 72
7.3 Data quality processes ..... 73
7.3.1 Medrio EDC ..... 73
7.3.2 KCTU Randomisation System ..... 73
7.3.3 Q-Interactive ..... 73
7.4 Database lock ..... 74
7.4.1 Medrio EDC ..... 74
7.4.2 KCTU Randomisation System ..... 74
7.4.3 Q-Interactive ..... 74
7.5 MRI data management and storage (CONNECT) ..... 74
**8 Summary of known and potential risks of Triptorelin ..... 75**

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

8.1 Side effects commonly reported ..... 75
8.2 Common side effects of Triptorelin ..... 75
8.3 Uncommon and rare side effects of Triptorelin ..... 76
8.4 Side effects with unknown frequency of Triptorelin ..... 76
8.5 Side effects of other GnRHa preparations ..... 76
8.6 Treatment Interactions ..... 77
**9 Adverse Event Management and Reporting ..... 77**
9.1 Reference Safety Information ..... 78
9.2 Evaluating AEs and SAEs ..... 78
Assessment of intensity ..... 78
Assessment of causality ..... 79
Assessment of expectedness ..... 79
Follow-up of AEs and SAEs ..... 80
Post-study AEs and SAEs ..... 80
9.3 Adverse event processing responsibilities ..... 80
**10 Toxicity Management ..... 81**
**11 Premature Termination of Trial ..... 81**
**12 Ethics Approval ..... 82**
12.1 Protocol amendments and version control of study documents ..... 82
**13 Statistical Methods ..... 82**
13.1 Trial ..... 82
13.1.1 Primary Outcome ..... 82
13.1.2 Secondary Outcomes ..... 82
13.1.2.1 Scales of Gender-Related Distress, Mental Health Symptoms and Physical Health measures : ..... 82
13.1.3 Scales of Suicidal Ideation, Hospitalizations, Mood Symptoms, Behavioural and Functional Difficulties: ..... 83
13.1.4 Experiences of Therapeutic Options: ..... 83
13.1.5 Cognitive Assessments ..... 83
13.1.6 Continuous Physical Measures ..... 83
13.1.7 Binary Physical Outcomes ..... 83
13.2 HORIZON INTENSIVE ..... 83
13.2.1 Primary Outcome ..... 83

13.2.2 Scales of Gender-Related Distress, Mental Health Symptoms and Physical Health measures: ..... 84
13.2.3 Rates of Suicidal Ideation, Non-Suicidal Self-Injury, Hospitalizations, Mood Symptoms, Behavioural and Functional Difficulties: ..... 84
13.2.4 Experiences of Therapeutic Options: ..... 84
13.2.5 Cognitive Assessments: ..... 84
13.2.6 Continuous Physical Measures: ..... 84
13.2.7 Binary Physical Outcomes: ..... 84
13.3 CONNECT ..... 85
13.4 Sample size justification ..... 85
13.4.1 Trial ..... 85
13.4.2 HORIZON INTENSIVE ..... 86
13.4.3 CONNECT ..... 86
13.5 Statistical methods for primary and secondary outcomes ..... 86
13.5.1 Statistical methods for primary outcome ..... 86
13.5.1.1 Trial ..... 86
13.5.1.2 HORIZON INTENSIVE ..... 88
13.5.1.3 CONNECT ..... 88
13.5.2 Statistical methods for secondary outcome ..... 88
13.5.2.1 Continuous outcomes ..... 88
13.5.2.1.1 Trial ..... 88
13.5.2.1.2 HORIZON INTENSIVE ..... 88
13.5.2.2 Binary outcomes ..... 88
13.5.2.2.1 TRIAL ..... 88
13.5.2.2.2 HORIZON INTENSIVE ..... 89
13.5.3 Statistical methods for exploratory analyses ..... 89
13.5.3.1 CONNECT ..... 89
13.6 Adherence ..... 89
13.7 Interim analyses (statistical) ..... 89
13.8 Methods for additional analyses (e.g. subgroup analyses) ..... 90
13.9 Methods to handle missing data ..... 90
13.10 Populations under investigation ..... 90
13.10.1 TRIAL ..... 90
13.10.2 HORIZON INTENSIVE ..... 90

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

13.11 Methods to handle compliance ..... 90
13.12 Sensitivity analysis..... 91
13.13 Plans to give access to the full protocol and participant-level data ..... 91
**14 Oversight and monitoring..... 91**
14.1 Programme Management Group (PMG)..... 91
14.2 Programme Steering Committee (PSC) ..... 91
14.3 Data Monitoring Committee (DMC)..... 92
14.4 Monitoring ..... 92
**15 Miscellaneous..... 92**
15.1 Plans for independent audit ..... 92
15.2 Dissemination plans..... 92
15.3 End of trial ..... 92
15.4 Confidentiality ..... 93
15.5 Funding ..... 93
15.6 Availability of data and materials ..... 93
15.7 Insurance and indemnity ..... 94
15.8 Archiving ..... 94
**16 References..... 95**

APPENDIX A - Individual Schedule of Events.....98
APPENDIX B – Data Flow.....109
APPENDIX C - Alternative IMP Preparation Flowchart.....110
APPENDIX D – Side-effects of alternative GnRHa.....111

# 1 Introduction

## 1.1 Studies included in this protocol

This protocol includes the rationale for and conduct of three inter-related studies in the PATHWAYS Programme: PATHWAYS TRIAL, PATHWAYS HORIZON INTENSIVE and PATHWAYS CONNECT.

## 1.2 Background and rationale

PATHWAYS is a programme of inter-related research studies whose ultimate aim is to improve the care of children and young people (CYP) presenting to clinical services with gender incongruence.

Gender incongruence is characterised by a marked and persistent disparity between an individual's experienced gender and the birth-registered sex, which may lead to a desire to 'transition', to live and be accepted as a person of the experienced gender[1]. Gender incongruence may be more distressing during significant transitional life stages such as adolescence, which can lead to gender dysphoria[2].

### 1.2.1 Epidemiology and presentation to services

Until recently, gender incongruence was considered rare[3] with limited clinical awareness and service provision. Figure 1[4] depicts the 20-fold increase in UK referrals between 2009 and 2021.

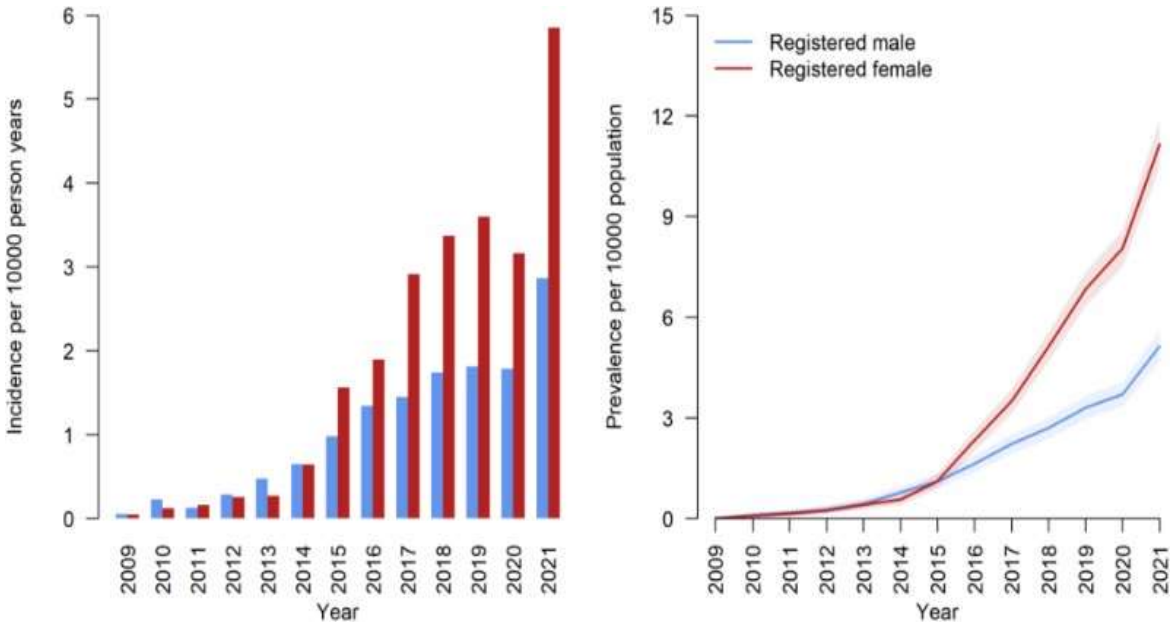



**Figure 1 -** The characteristics of young people seeking support in the United Kingdom (UK) have also changed over this time period. This means that the results of studies reporting on earlier cohorts of CYP may not apply to those currently accessing gender services.

### 1.2.2 Puberty suppression and changes in care

Over the past two decades, changes in the age of presentation, ratio of male-female birth-registered sex and prevalence of people presenting with gender incongruence have coincided with changes in the available treatment, most notably the use of puberty suppression which had not previously been used for this purpose. Puberty-suppressing hormones or gonadotropin-releasing hormone analogues (GnRHa) came into use in some countries with several potential indications for their use. GnRHa has a number of licensed indications, including its use for precocious puberty, where the aim is to arrest abnormally early onset of puberty. Other indications include endometriosis and prostate cancer in adults, and menstrual suppression in acute oncology settings. Several possible benefits of GnRHa were hypothesised for CYP experiencing gender incongruence. These included reducing feelings of distress with one's body developing secondary sexual characteristics (body dysmorphia) and related emotional distress and making any subsequent physical transition to the opposite gender more straightforward, potentially with less radical surgery. It was also hypothesised that puberty suppression would provide children and young people (referred to hereon as CYP) 'time to think' without further pubertal development to explore gender identity as part of normal adolescent exploration. However, a systematic review reported that as few as 0-8% (including 2% of UK youth[4]) receiving GnRHa subsequently desisted from the treatment and a transitioning pathway[5]. This rate of gender transitioning was substantially higher than those reported from earlier observational studies, prior to the use of GnRHa[3]. This raised concerns about whether the intervention might itself be narrowing rather than increasing perceived choices regarding gender identity.

The observed changes in the population of CYP presenting at Gender Services, in terms of age, birth-registered sex and neurodevelopmental traits or disorders, means that clinical experience from and longitudinal follow-up earlier cohorts may not be applicable to the group of young people currently seeking care. Hence new research studies are needed.

GnRHa has become part of routine care for gender incongruence in some settings without the standard of rigorous evaluation of benefits and risks, including randomised clinical trials (RCTs)[5]. Its use has elicited differing and often strongly held- and polarised views about the optimal treatment pathway for CYP with gender incongruence and specifically about the benefits and safety of GnRHa to suppress puberty. At one extreme, some argue that their use is 'life-saving' for those with high levels of distress about the gender and bodily changes. Proponents have argued (without basis[6]) that suicide rates have increased since the UK implemented a ban on the use of GnRHa for this indication. At the other extreme, it has been alleged that GnRHa has long-term physical adverse effects and disrupts what should be psychological exploration of gender and gender distress.

Gender incongruence is often a lifelong condition in which the ultimate aim of intervention is to promote long-term well-being and good psychosocial and

psychosexual functioning over the life-course. However, there has been a lack of high-quality longitudinal studies with sufficient retention rates to inform clinicians and patients about long-term outcomes, both for those who opt for medical care pathways and those choosing alternatives[5, 7, 8].

When used GnRHa is often part of a wider therapeutic approach to gender incongruence. Non-medical care for CYP experiencing gender incongruence include psychosocial interventions aimed at exploring gender (and often wider) identity and promoting positive self-esteem, good psychosocial functioning, and well-being. However, non-endocrine intervention for CYP with gender incongruence have similarly not been subjected to rigorous evaluation. As highlighted below, many CYP experiencing gender incongruence are neurodiverse and/or have had adverse childhood experiences whose impact on their identity and psychosocial functioning need addressing as part of holistic, comprehensive care. While there is robust evidence for interventions/management strategies around neurodivergence and adverse childhood experiences, their application in the context of gender incongruence may require specific adaptations and bespoke evaluation.

Hence currently decisions about care are made in the context of very limited evidence and against a background of strong personal preferences. This is particularly pertinent for a condition in which intervention decisions rely heavily on the preferences of relatively young children and adolescents who are at a developmental stage intrinsically characterised by exploration of personal identity. Many healthcare professionals and parents/caregivers have expressed concerns about over-reliance on the views of CYP at this dynamic and formative developmental stage and request clearer and more objective clinical evidence to guide decision-making in the interests of longer-term positive outcomes.

Because of the range of presentations, experiences and care needs, the developmental trajectories into adult life may well be different for CYP who experience gender incongruence. These differences may be across all developmental areas: physical and mental health, cognition and life experiences. Hence a comprehensive understanding of care needs and benefits and risks of different treatment approaches will need to include a longitudinal study of CYP with gender incongruence who receive different types of intervention.

## 1.3 Summary of PATHWAYS Research Programme

The PATHWAYS research programme includes five inter-related studies designed to increase our understanding of gender incongruence amongst CYP and its longitudinal course. The full programme is outlined here to provide context for PATHWAYS TRIAL, PATHWAYS HORIZON INTENSIVE and CONNECT, which are the subject of this protocol.

All the PATHWAYS workstreams, bar PATHWAYS Engagement, involve CYP and their parents/carers/legal guardians who are attending the NHS Gender Services for Children and Young People (CYPGS).

## The overarching aims of the PATHWAYS research programme are:

1) To determine the short/medium-term benefits and risks of GnRHa for puberty suppression, across psychosocial, physical, cognitive and brain outcomes, in CYP with gender incongruence.
2) To understand the care needs and experiences of CYP with gender incongruence that are associated with using GnRHa or not through longitudinal quantitative and qualitative studies.
3) To continue to involve CYP with gender incongruence and their parents/carers/legal guardians in designing, implementing and interpreting the research to ensure this study addresses their needs and can inform planning and data collection in any longer-term follow-up.

**Studies within the PATHWAYS Programme:**

### 1.3.1 PATHWAYS HORIZON

PATHWAYS HORIZON is an observational cohort (n~3600) of all CYP attending the CYPGS. HORIZON participants will be asked to complete questionnaire measures about their experiences, mental health, and quality of life on an annual basis throughout the course of the study. The study will last for the duration of the funding period (5.5 years).

### 1.3.2 HORIZON INTENSIVE

In addition, we will recruit 300 CYP to HORIZON INTENSIVE. HORIZON INTENSIVE participants will be recruited from the HORIZON cohort and will be broadly matched to those participating in TRIAL (below) on clinical centre, birth-registered sex, presence of a neurodevelopmental disorder or high level of traits and chronological age. They will be asked to complete all the same measures as PATHWAYS TRIAL including the physical health assessments except that physical health, cognitive and brain imaging measures will only be undertaken at baseline and endpoint. The PATHWAYS HORIZON INTENSIVE protocol is included in the PATHWAYS TRIAL protocol and application.

### 1.3.3 PATHWAYS TRIAL

PATHWAYS TRIAL is a trial of GnRHa in the management of gender incongruence in children and young people.

### 1.3.4 PATHWAYS CONNECT

PATHWAYS CONNECT looks at outcomes relating to cognition and brain development in CYP attending the services, including those who are and are not receiving GnRHa.

### 1.3.5 PATHWAYS VOICES

PATHWAYS VOICES uses longitudinal qualitative interviews to explore the needs and care experiences of CYP and their families and how these change over the course of time / treatment.

### 1.3.6 PATHWAYS ENGAGEMENT

PATHWAYS ENGAGEMENT is an advisory group of young adults >18 years, adults with gender incongruence, and parents/carers/legal guardians who will advise on all aspects of the programme, including outcome measures, patient involvement in research and strategies for long-term patient engagement, interpretation, and communication of findings. Members of PATHWAYS ENGAGEMENT will meet in person in London and/or online for briefer meetings. NB: As an advisory group of experts by experience, ethical approval will not be sought.

## 1.4 Relationship between PATHWAYS studies

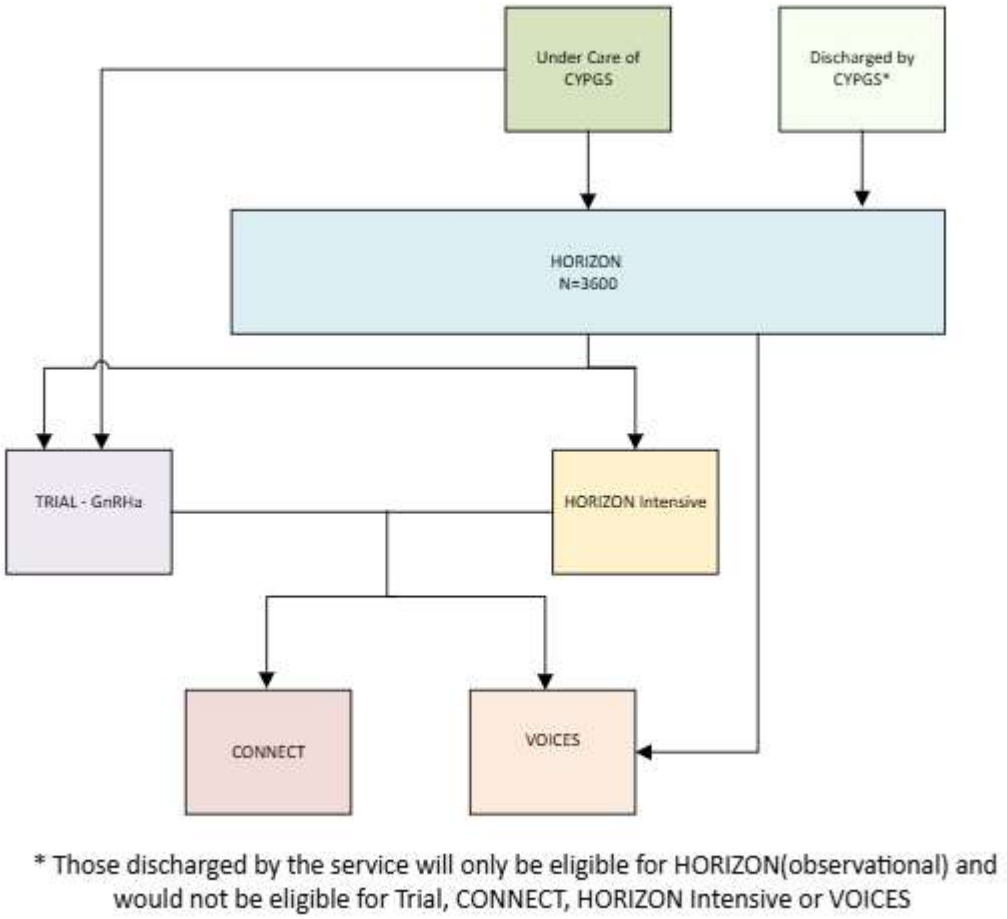



***Figure 2. Overlap between PATHWAYS participants in different studies***

***Table 1.*** *Relationship between PATHWAYS protocols and participant groups*

| **Study Protocol** | **Participant group** | | |
|---|---|---|---|
| | Trial immediate start | Trial delayed start | HORIZON INTENSIVE |
| Trial | 113 | 113 | 300 |
| ⬇ | ⬇ | ⬇ | ⬇ |
| CONNECT | 75 of 113 | 75 of 113 | 100 of 300 |

All CYP attending the CYPGS will be eligible for PATHWAYS HORIZON. We anticipate ~80% of CYP will assent/consent to HORIZON. Only CYP who assent/consent (and provide parental consent) to PATHWAYS HORIZON will be approached for PATHWAYS HORIZON INTENSIVE. Many CYP subsequently deemed eligible for and enrolling in PATHWAYS TRIAL will first be members of PATHWAYS HORIZON. Once they join PATHWAYS TRIAL, they will become part of that study and data collection will follow that protocol (rather than the PATHWAYS HORIZON protocol). CYP attending the CYPGS who decline participation in HORIZON but are deemed eligible for PATHWAYS TRIAL may join that study once they provide assent/consent. CYP participating in PATHWAYS VOICES are drawn from those in PATHWAYS HORIZON considering GnRHa (and hence may become members of TRIAL). **Figure 2** depicts the relationship and participant overlap between studies.

### 1.5 Rationale for a Randomised Controlled Trial

RCTs are the gold standard method to determine the causal role of any treatment in relation to observed benefits and harms[9]. While observational studies have been used to explore efficacy and side effects, it is well-recognised that the estimates arising from such studies are often biased (usually but not always in favour of increased efficacy and fewer adverse effects) because of patient selection and inability to fully account for confounding effects. In gender medicine and studies of GnRHa, a common confounder is the co-occurrence of psychosocial and endocrine care where specific effects cannot be determined out in observational studies. While the pre-eminence of RCTs is generally well-recognised, due to the controversial nature of this intervention and research in this field, the scientific and ethical rationale for an RCT is outlined here.

#### 1.5.1 Clinical equipoise

The ethical basis of all RCTs is clinical equipoise, that is, the balance of benefits and harms of an intervention is uncertain and reasonably balanced between the intervention arms. While many claims have been made about benefits and harms of GnRHa, depending on the perspective of the proponents, a recent systematic review of interventions to suppress puberty[7] highlighted the general low- to medium-quality of the available evidence. No previous RCTs were identified. In particular, in relation to mental health, psychosocial functioning and quality of life there was inconsistency

among studies showing either some improvement or no change with initiation of GnRHa. With regard to possible physical harms, studies show decreased age-standardised bone mineral density with GnRHa; however, there is an absence of follow-up to determine whether these changes are persistent after ceasing GnRHa and/or commencing on gender affirming hormones. There has been speculation about cardiovascular harms, but there is no evidence to support this.

### 1.5.2 Retrospective studies.

Retrospective studies are a form of observational study looking at earlier data in a cohort of individuals. They are used to identify potential causal factors that can be formally tested in more rigorous designs. Retrospective studies have all the drawbacks of prospective observational methods, outlined above. They also require that relevant data were collected at earlier timepoints.

It has been suggested that UK research on GnRHa for puberty suppression in gender incongruence might start with a retrospective study of the young people previously seen at the Tavistock Service who are now young adults. It would not be possible to address important questions about GnRHa for several reasons. First, clinically recorded information on this patient cohort was not standardised or recorded at specific timepoints. Second, published reports from this cohort suggest high levels of attrition which are likely to be biased in relation to clinical outcomes. Third, some important classes of data, including cognition, childhood adverse experiences and neurodiversity, were not recorded at all. Hence, we conclude that a retrospective study would not provide alternative evidence.

### 1.5.3 Must the research be undertaken with children and young people, who are a vulnerable population?

Ethical considerations dictate that research should only involve vulnerable populations such as children and young people when the research question cannot be adequately addressed with an alternative population or study design. In this instance, suppressing puberty as a component of intervention for gender incongruence can only be performed during puberty, limiting it to adolescents. While due care and attention should be applied when considering research in children and young people, we also note that the failure to undertake research has disadvantaged their health. For example, cancer outcomes in young people lagged behind those in adults until there was a concerted effort to develop and test new interventions for childhood cancers.[10, 11]

### 1.5.4 Long-term benefits

Gender incongruence can be a long-standing, even life-long, experience. Hence, it is important to ensure long-term follow-up of any interventions in childhood and adolescence, to understand their impact in adult life. It has been suggested that a short-term clinical trial lasting for 2 years will not help to address the question of whether GnRHa is beneficial. This is incorrect for several reasons. First, one of the reasons for offering GnRHa is to manage immediate (short-term, during treatment)

levels of emotional distress regarding pubertal changes and allow young people time to explore their identity. However, the currently available evidence (described above) is inconsistent in whether GnRHa has positive short-term benefits. An RCT of limited duration can answer these questions. Second, long-term effects can only be evaluated following research examining short- or medium-term effects. There are many examples of this in relation to lifelong conditions. For example, it was important to document the short-term benefits of stimulant medication in ADHD before examining longer-term effects.

**In summary**, an RCT of GnRHa in children and young people with gender incongruence is ethically sound because of clinical equipoise and the need to conduct the study in this age group. The study is rigorous in eliciting clinical eligibility and informed assent/consent., processes to safeguard the best interests of children and young people, described below. Alternative study designs are not able to provide the needed quality of evidence to determine the benefits and harms of this intervention.

## 2 Trial Design

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

As each participating CYP reaches endpoint, they will decide, with their parents/legal guardians and health-care professionals, including paediatric endocrinology, what further interventions, if any they wish to pursue. This may include remaining on GnRHa, moving to cross-sex hormones, or stopping/pausing GnRHa.

HORIZON INTENSIVE is a non-randomised comparison group of CYP not receiving GnRHa who are broadly matched on key participant characteristics. They will complete the same physical, physiological and cognitive measures as TRIAL participants, although only at baseline and endpoint. As CYP who experience gender incongruence may differ from the general population of same-aged CYP, these data will provide a comprehensive comparison to aid interpretation of the effects of GnRHa.

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

## 2.1 Rationale for Trial Design

It is generally considered that the most robust randomised controlled trial design is (a) placebo-controlled and (b) double-blind. While there are many examples of alternative designs, it is nevertheless important to justify any deviation from this gold standard.

### 2.1.1 Why not use a placebo-controlled, double-blind design?

*It is not possible to blind GnRHa treatment for any significant period of time.* Puberty suppression (or its absence) cannot be blinded for any significant period of time. While the onset and rate of puberty shows considerable inter-individual variation, the purpose of this intervention is to stop puberty during the time period when its effects would be most obvious, during the development of secondary sex characteristics. Hence any advancement of puberty would be obvious to the young person, thus unblinding them to treatment allocation. For post-menarcheal females, puberty suppression stops periods, in both arms identifying treatment allocation. Treatment for puberty suppression typically lasts for several years, so no young person would remain blind.

*In the absence of blinding for any period of time, is there benefit to using a placebo?* For all bar post-menarcheal females, it is possible young people would be blinded to treatment for several months, so that initial measured outcomes might be masked to treatment arm. This would be an important consideration if very short-term effects were of particular interest, although this would need to be balanced against inconvenience for patients in attending hospital for sham injections. It would be unclear when and whether to stop sham injections as unblinding would likely occur at varying points for different patients.

*Knowledge of the intervention is part of the effect.* Finally, part of the potential benefit (to be studied) of GnRHa, is patients' knowledge that their puberty is being suppressed. The efficacy of GnRHa in suppressing puberty is not being assessed in this study, because this is well-documented as highly efficacious in this regard. The question is whether patients have better psychological outcomes, including higher quality of life, reduced mental health symptoms when they stop experiencing ongoing development of puberty. There are also important questions to be addressed about physical and cognitive effects in the short- and medium-term as well as longer-term benefits and risks.

*Summary.* For these reasons, blinding and placebo-control are not only unlikely to achieve their aims, but they would potentially miss possible short-term benefits of the intervention that need to be measured in providing a comprehensive picture of benefits and risks.

## 2.2 Choice of immediate vs delayed treatment arms.

A delayed start comparison provides three time points within the trial: baseline, midpoint, when the immediate start but not the delayed start have received the

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

intervention, and endpoint, when both have received the intervention but for different lengths of time (see flow chart). Midpoint results provide the comparison of GnRHa vs no endocrine treatment while endpoint results provide insights into the effects of timing of GnRHa and its cumulative effects. For midpoint results, therefore, the length of the delay is critical to ensure the two arms have sufficient time to diverge, for both positive and potential adverse effects, while not being so long that CYP complete pubertal development.

We hypothesise two main effects driving outcomes:

1. Early benefits, which may or may not endure. This will include the expectancy effects of the perceived benefits of GnRHa, mainly affecting symptoms of anxiety, depression and suicidality. We will obtain a baseline measure of the strength of preference for immediate vs delayed intervention and measurement of the above traits (RCADS and ASQ, Schedule of Events) after informing participants of their trial allocation and before GnRHa injection. Participants randomised to a delayed start and expressing a strong preference for immediate intervention may show deterioration from their baseline scores. Expectation effects could be short-lived for the immediate-start group, with scores regressing to baseline. It is also possible that GnRHa leads to a more consistent reduction in distress, which allows CYP to make real gains in other aspects of psychosocial function, including improved self-confidence, peer relations, school engagement and learning (all nominated by CYP as important outcomes). To track this, we will continue to obtain the RCADS and ASQ at 3, 6, 12, (midpoint) 15 and 18 months. These immediate benefits will show the greatest separation between groups at the midpoint assessment.
2. Effects that reflect cumulative disruption of puberty development. These are most likely to be ones where the direct effects of hormones come into play, e.g., normative development of bone density, height and potentially cognition and brain development. Here we would expect not only do the groups to diverge at the midpoint, but also, potentially, retain the slope related to the effect of puberty suppression, with greater endpoint effects on those having an immediate start and potentially those who are earlier in puberty (and therefore have more disruption. These will be exploratory analyses.

*Does one year provide a sufficient delay to see a divergence between arms?* In terms of physical effects, studies that have measured yearly bone mineral density after starting GnRHa find significant decreases in age- normed z-scores by one year[12, 13]. It is more uncertain whether this time frame is sufficient to show differences in mental health/psychosocial and cognitive outcomes are more challenging because of inconsistencies in the available studies. The UK study had serial measures and failed to find significant improvement over time, e.g., at 12, 24 and 36 months[14-16]. Hence this does not suggest that a longer duration of delay would necessarily produce greater separation between arms. In contrast, another study with serial

measures of anxiety and depression over the first year of intervention with either puberty suppression or cross-sex hormones found significant improvements in anxiety and depression at 3, 6 and 12 months and also in comparison to those not initiating endocrine intervention[16]. While imperfectly controlled for other interventions and group characteristics, this suggests that self-reported changes may occur early on.

In the general population, clinical trials of pharmacological or psychological interventions report significant reduction in anxiety[17] or depression[18] over 3- to 6-month periods, demonstrating the shiftability of these symptoms over this time frame.

In relation to cognition, the pre-post studies of IQ in those treated with GnRHa for precocious puberty[19] or gender dysphoria[20] report changes over more than 2 years, and the timing of such changes is not clear. The only study to examine cognition over time in those receiving GnRHa reported an association between worse parent-reported executive function and receiving GnRHa for longer ( ≥1 (vs <1) year)[21].

## 2.3 Intervention Delivery and Monitoring

The trial intervention has been designed to mirror clinical routine practice as closely as possible. To achieve this, we have drawn on the experience of paediatric endocrinologists who delivered this intervention prior to the UK ban as well as those from other countries where the intervention is currently being used for this indication. Hence the choice of GnRHa compound and administration schedule reflects common practice amongst paediatric endocrinologist for this indication. The monitoring of physical health, including considerations for eligibility and frequency of repeat evaluations, also reflects routine clinical practice. The consideration of safety investigations is based on the products' paediatric Summary of Product Characteristics (SmPC), according to the licensed use for precocious puberty. This is augmented by additional possible safety concerns related toits use during adolescence in disrupting otherwise normal pubertal development. This means that the results of this trial could be directly applicable to everyday clinical care, should such a policy decision be made at the end of the trial. Additional measures that are not part of routine clinical practice include questionnaires that monitor mental health, quality of life and well-being, and the measures of brain development through MRI and cognitive assessments.

## 2.4 Objectives

### 2.4.1 Primary Objective

To determine the short/medium-term benefits and risks of GnRHa for puberty suppression in CYP with gender incongruence. This will take a comprehensive approach to domains of possible benefit and risk, including quality of life, mental

health, gender identity/dysphoria and body satisfaction, impact on cognition and brain development and physical effects including bone mineral density. For the purposes of this study, short-term refers to effects during the early stages of intervention, e.g., typically in the first three to six months while medium-term refers to effects at the trial endpoint

### 2.4.2 Secondary Objectives

The secondary objectives of this study are:

1. To understand which potential outcomes e.g., (domains of quality of life, mental health, gender and body distress, cognition, physical health) are the priority goals for CYP receiving GnRHa.
2. To describe the characteristics of those seeking GnRHa:
    I. Evaluate Psychosocial Functioning:
    II. Assess Mental Health Outcomes:
    III. Examine Gender Dysphoria and Body Image:
    IV. Monitor Physical Health and Development:
    V. Understand Cognitive and Brain Development:
    VI. Explore Safety and Adverse Events:
    VII. Investigate Fertility Preservation Decisions:
    VIII. Understand the Role of Neurodevelopmental and Mental Health Diagnoses:
    IX. Assess the Impact of Social and Environmental Factors:
3. To describe what decisions CYP make at the end of GnRHa in terms of gender care, including remaining on GnRHa, moving to cross-sex hormones, or stopping/pausing endocrine interventions.
4. To link trajectories of brain development to cognitive measures, including general intelligence, memory and executive function.
5. To engage CYP and their parents participating in TRIAL and HORIZON INTENSIVE in the study methods and findings in order to promote longer-term follow-up that will provide an opportunity to understand their choices around gender identity and gender care, as well as their outcomes in the above domains as they enter adult life.

### 2.4.3 Exploratory Objectives

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

# 3 Participants

## 3.1 Study setting & recruitment

Participants will be identified through the NHS England Gender Services (GS). Participants may already have enrolled in HORIZON or not; this will make no difference to their eligibility.

## 3.2 Eligibility criteria for TRIAL

The research team will only approach participants who have been identified as clinically eligible for GnRHa (below). Specifically, the research team will not attempt to increase the number of cases considered clinically eligible or to influence the views of clinicians regarding eligibility in any way.

All CYP who are considered clinically eligible for GnRHa will be approached to provide them and their parents/legal guardians with specific information about the trial. This eligibility will apply regardless of whether they have previously consented to any PATHWAYS studies, specifically PATHWAYS Horizon. Because inclusion in the trial is currently the only avenue to receive GnRHa in the UK, this will be made clear to CYP and their parents/carers/legal guardians attending the service, through information provided at routine clinic visits, through early information sessions with members of the endocrine service and via the study website. Thus, those who are being considered for clinical eligibility will be aware that they would then need to assent/consent to the trial.

### 3.2.1 Clinical eligibility for GnRHa

Clinical eligibility will be considered first by the clinical care team and then by the CYPGS National Multi-Disciplinary Team (NMDT), the latter to ensure that there is a consistent approach across clinicians and services. Below are the criteria that will be assessed by the clinical services and NMDT prior to consideration for inclusion in the research trial.

If recruitment rates fall below expectations, clinicians will not be pressured to identify additional participants. Instead, we will explore with the funder the possibility of extending the recruitment period or employ probabilistic and Bayesian statistical methods to ensure the robustness and clarity of our findings.

#### 3.2.1.1.1 CYPGS NMDT

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. Only CYP who have received approval from the NMDT for GnRHa to be considered will be approached for TRIAL.

#### *3.2.1.2 Clinical Inclusion Criteria*

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

i. There will be written information provided and recording of how the child or young person flexibly demonstrates an understanding of possible risks and benefits.
ii. Information may also be provided in other, additional formats that are bespoke for the individual child or young person's cognitive and learning style. For example, this may include visual supports and audio recordings.
iii. The child or young person will be asked to explain their understanding of treatment with GnRHa in their own words.
iv. A checklist will be used by the clinical services to ensure all key points have been covered and understood.

b. Fertility preservation will have been discussed with each CYP, with developmentally appropriate and/or adapted language/ other forms of communication (as described above) descriptions of what would be involved, how it can be accessed, and the potential long-term implications if fertility preservation is not accessed. CYP will not be referred to the Trial until the NMDT is satisfied this has been adequately considered.

8. At least one parent or legal guardian:
   a. demonstrated sufficient understanding of the nature and purpose of the proposed treatment, including the possible advantages and disadvantages of the treatment such as immediate psychological impacts and long-term implications, specifically including fertility preservation options, in the context of their CYP's personal situation and needs. This should also include the fact that there may be risks or benefits that are currently unknown.
   b. demonstrated that they can retain the key parts of that relevant information for a sufficient period to enable them to use and weigh that relevant information to give their informed consent to the proposed intervention.
9. The CYP and parent(s)/legal guardian(s) are willing to be randomised into either study arm, documented by signed informed consent (parent/guardian) and assent (CYP).

#### *3.2.1.3 Clinical Exclusion Criteria*

1. Physical conditions where puberty will not commence or advance in a patient. This may include gonadal failure (e.g. due to genetic disorders such as Turner syndrome) or central hypogonadotropic hypogonadism.
2. Unstable physical health. The purpose of this criterion is to ensure that that the CYP is not undergoing concurrent high-intensity physical interventions which might affect their response to GnRHa or their ability to adhere to the trial protocol. These include but are not limited to:
   a. Very low or very high BMI (or rapid changes in BMI), particularly if there is a concerning trajectory or associated nutritional or metabolic concerns. This could include eating disorders or body dysmorphic disorder.

   b. Any poorly controlled medical disorder, such as uncontrolled epilepsy, inflammatory bowel disease, cystic fibrosis. This includes any other condition where participation may pose a risk to the individual's health or compromise study integrity.
   c. Concerns about bone health or significant risk of fractures (this may also include a low baseline bone density).
   d. QTc interval above 470 milliseconds at screening, or concomitant high-risk QT-prolonging drugs that cannot be ceased
3. Hypersensitivity to gonadotropin releasing hormone (GnRH), its analogues, or to any of its excipients
4. Known congenital long QT syndrome
5. Unstable mental health that may impair ability to provide informed assent/consent or lead to risk of serious harm to self or others. Many CYP with gender incongruence experience anxiety and/or depression which they relate to gender dysphoria or distress. It is not the intention to exclude those with mild to moderate levels of mental health symptoms. However, severe or unstable symptoms may affect the ability to engage in all aspects of the clinical protocol. Examples would include (but are not limited to):
   a. Severe or profound depression with significant effects on the ability to accurately evaluate choices and future outcomes;
   b. Severe body dysmorphic disorder that is confounded with secondary sexual characteristics or physique not conforming to the desired gender;
   c. Active psychotic symptoms;
   d. Significant risk of harm to self or others as exemplified by consistent suicidal thoughts, repeated and ongoing acts of self-harm and/or the need for emergency plans with the child or young person and family;
6. Aspects of family/home situation that makes it likely the CYP will not be able to adhere to aspects of the protocol such as attending regular follow-up appointments. This last requirement will have been assessed in relation to the CYP's ability to find ways of attending appointments in the CYPGS.
7. Clinical concerns about the young person's capacity to consent.
8. Insufficient understanding of PATHWAYS TRIAL.
9. New or ongoing safeguarding concerns.
10. Birth-registered females with undiagnosed vaginal bleeding.
11. Birth-registered females who are pregnant or lactating.
12. Individuals of child-bearing potential (i.e. sexually active birth-registered female not using effective contraception as compatible with GnRHa**) who are at risk of pregnancy during the trial.

Of note, whilst not an exclusion criterion, the clinical teams will strongly counsel against smoking or nicotine-containing vaping for GnRHa due to its contraindication with starting oestrogen or testosterone and its negative impact on bone health.

* POCBP defined as: fertile and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral

oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

** Effective methods of contraception for use in TRIAL include:

- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

Participants will be reminded at the final visit of the importance of continuing non-hormonal methods of contraception (i.e. barrier contraception) until menses return.

Whilst PATHWAYS TRIAL does not include a set plan for diet or exercise, we do encourage participants to keep up healthy habits during the study. This means staying active, eating a balanced range of foods, and looking after their general well-being. Keeping physically active, especially including walking or running, is particularly important as it can help support bone health while puberty is paused. Some CYP may notice changes in their weight during treatment, and maintaining healthy routines can help manage this.

#### *3.2.1.4 Research Inclusion Criteria*

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

#### *3.2.1.5 Research Exclusion Criteria*

1. The CYP has previously taken or is currently using GnRHa for this indication. This will be identified by (I) asking CYP and their parents/legal guardians about off-label use and (ii) through hormone blood tests at baseline (all participants) and for those randomised to delayed start at 12 months. Participants and their parents/legal guardians will be reminded about the safety and legal concerns of off-label use.
2. The CYP is or has taken cross-sex hormones for gender incongruence/dysphoria.
3. The participant is involved in another research trial*

* Specifically, a CTIMP or another intervention that could possibly interfere with involvement in PATHWAYS TRIAL or interpretation of the findings

Note. Sex steroids used in oral contraceptives either for birth control or management of dysmenorrhea is not an exclusion.

## 3.3 Eligibility Criteria for HORIZON INTENSIVE

CYP who are participants in PATHWAYS HORIZON will be eligible to take part in HORIZON INTENSIVE if they are not considered clinically eligible for GnRHa presently or in the future. Ineligibility may occur based on the preferences of the CYP and their parents/legal guardians or due to clinician view that they are not suitable for GnRHa either presently or in the future, and this view has been communicated to the CYP and their parents/legal guardians.

HORIZON INTENSIVE aims to include CYP with similar characteristics to TRIAL participants in relation to Gender Service of origin, birth-registered sex, Tanner stage and presence of neurodevelopmental disorders/high levels of traits. For initial identification, chronological age will be used as a proxy for Tanner stage, with self-reported Tanner stage acquired at baseline for matching purposes. Consideration will also be given to the amount of care they have received in the CYPGS so that this is roughly similar. To balance recruitment, the research team will identify from the research database potential participants to be approached for inclusion in HORIZON INTENSIVE. This selection will be informed by the above characteristics of TRIAL participants already recruited.

### 3.3.1 HORIZON INTENSIVE Inclusion Criteria

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

### 3.3.2 HORIZON INTENSIVE Exclusion Criteria

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

## 3.4 Eligibility Criteria for PATHWAYS CONNECT

As per Table 1 above, participants in TRIAL and HORIZON INTENSIVE will be recruited to CONNECT. For TRIAL participants, they will be told about CONNECT when they are approached for TRIAL and will need to join CONNECT prior to randomisation in order to have a baseline MRI scan. For HORIZON INTENSIVE participants, they will be told about CONNECT at the same time as being approached for joining HORIZON INTENSIVE from HORIZON.

### 3.4.1 PATHWAYS CONNECT Inclusion Criteria

1. Participant is a member of PATHWAYS TRIAL or PATHWAYS HORIZON INTENSIVE.
2. Participant is willing to participate in brain imaging study, including travelling to London (King’s College London).

3. Participant provides informed assent (for u16) or consent (for 16+).
4. Parent/legal guardian provides consent.

### 3.4.2 PATHWAYS CONNECT Exclusion Criteria

1. MR imaging is contra-indicated (e.g. ferro-magnetic metal implants).

## 3.5 Informed Consent

### 3.5.1 Informed Consent for TRIAL

#### *3.5.1.1 The process of determining clinical eligibility*

The process of determining clinical eligibility is set out in the clinical service document titled “PATHWAYS TRIAL for Gonadotropin Releasing Hormone Analogues (GnRHa) – Guidance for CYPGS clinicians” A schematic of the interplay between providing research information, determining clinical eligibility and then research eligibility is shown in Figure 3. This will involve a series of clinical meetings with the CYP both on their own and with their parents/caregivers/legal guardians focussing on known and unknown possible benefits and risks of GnRHa including possible longer-term risks, alternative interventions that may alleviate their symptom/distress. Information will be provided in written formats, supplemented with visual material and audio-recordings (e.g., of clinical discussions) adapted to meet the cognitive style of the CYP and their parents/caregivers/legal guardians. NHS interpreter services will be used for those who are not confident in their use of English. CYP and their parent/caregivers/legal guardians will be asked to demonstrate their understanding of GnRHa and alternative treatment approaches by answering questions from clinicians using their own words or alternative preferred communication (e.g., typing, audio recording). As part of the submission documents to the national MDT, CYP and at least one parent/legal guardian will be asked to provide their reasons for requesting GnRHa.

Specific attempts will be made to meet with both parents/legal guardians to elicit their independent views. Where there is a disagreement between parents/legal guardians about GnRHa, this will be flagged to the national MDT to consider in their decision.

While caregivers with parental responsibility will be encouraged to attend sessions to give their perspective and to support the CYP, it will be ultimately the views of parents and legal guardians whose views are formally considered in the clinical eligibility decision.

Fertility: The risks to long-term fertility will be discussed with each CYP considering GnRHa by a clinician in or attached to their Gender Service who has specific training and knowledge about fertility risks and options available to them as well as training in working with CYP experiencing gender incongruence. The information will include options around sperm donation and egg retrieval. CYP will be encouraged to ask questions and explore fertility preservation options prior to commencing on GnRHa

(if found clinically and research eligible). For those wishing to pursue fertility options at this time, a referral to specialist fertility preservation services will be facilitated by the Gender Service, noting that referrals are made either directly by paediatric endocrinologists or by the CYP's GP. There will be no upper limit imposed by research consent on how long young people have to consider and then explore fertility preservation options, and potential participants will be reminded of other constraints, e.g., around the upper age limit of the study.

Where there is clinical uncertainty about a CYP's suitability for GnRHa based on their physical health, e.g., low bone density, the relevant physical investigations will be undertaken prior to presentation at the NMDT, considered as screening investigations.

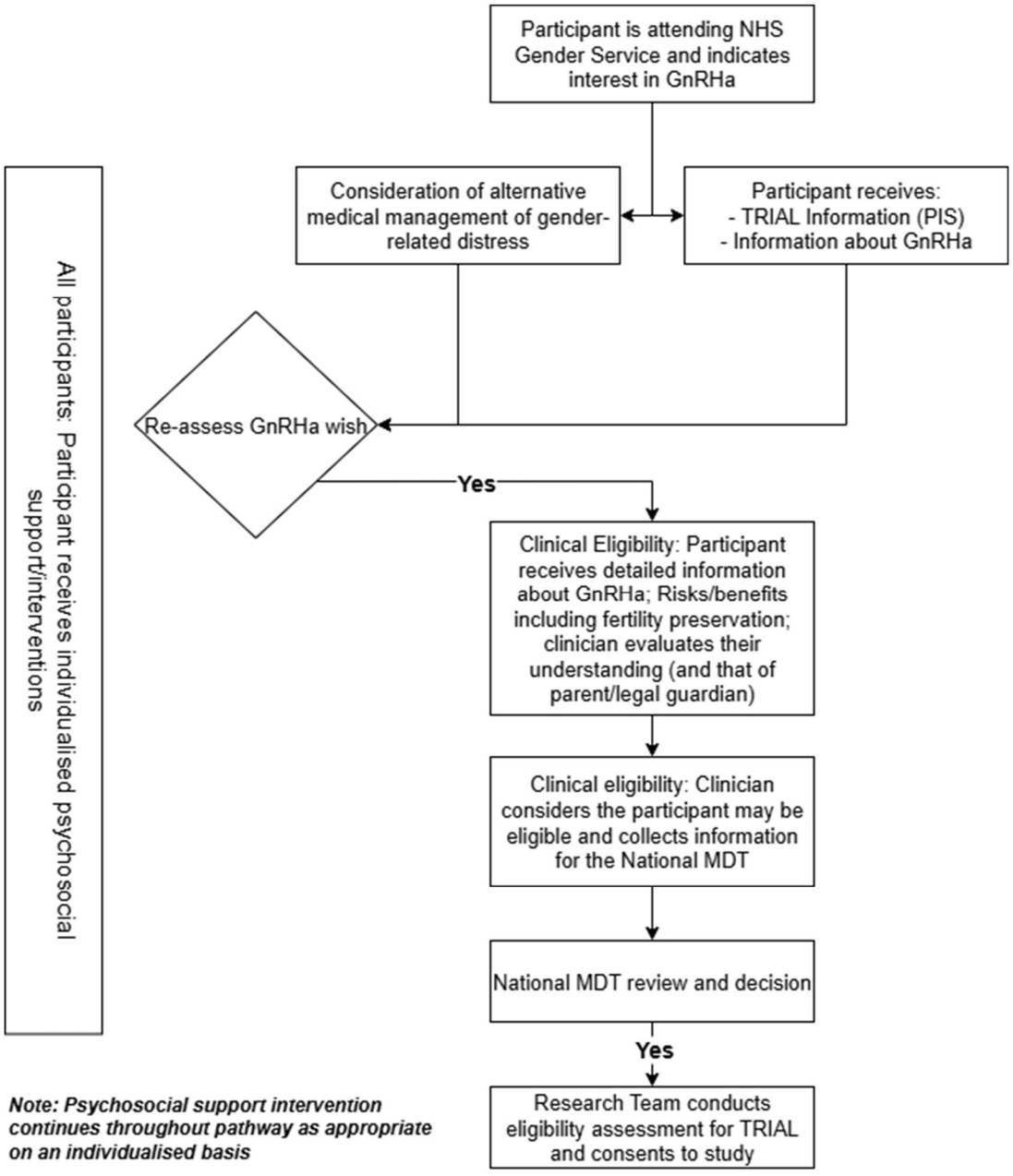



**Figure 3. Pathway to TRIAL Eligibility**

#### *3.5.1.2 The process of informed consent to participate in TRIAL*

CYP deemed clinically eligible for GnRHa and providing verbal consent to be contacted, will be contacted by the research team. The research team will confirm that the national MDT checklist was fully completed prior to the national MDT decision.

CYP and their parents/legal guardians will initially receive the standard paper PIS in clinic, but this may be supplemented by information in bespoke formats, to support the individual cognitive and learning styles of CYP and parents/legal guardians. CYP will be encouraged to read this information together with their parents/caregivers/legal guardians, prior to discussing it with a clinician in clinic. Specifically, researchers will check whether any bespoke sources of information were used to support the CYP's discussions with their clinical team in preparation for the clinical eligibility review by the national MDT. These information supports can be re-used and extended as needed by the CYP and their parents/legal guardians.

Following receipt of the information sheets, CYP and their parents/ legal guardians will discuss their participation with the Principal Investigator (PI) or delegated sub-investigator (SI) with GCP training. The PI/SI will further explain the purpose of the trial, the research procedures, and the potential benefits and harms associated with GnRHa, including possible long-term risks, and will establish the CYP and their parent/ legal guardian's comprehension of the information. The uncertainty about impact on long-term health and the importance of signing up to the NHS Registry to provide health information into adult life will be explained. This will usually involve seeing the CYP on their own in part, i.e., without a parent/legal guardian present. The CYP may have their clinical keyworker from the CYPGS present for additional support if they wish. Both parents/legal guardians are encouraged to be involved in the consenting process, where appropriate, and with at least one parent/legal guardian accompanying the CYP to ensure a supportive environment. While caregivers without parental responsibility may attend the meetings with the medical investigator, it will be made clear that it is only parents/legal guardians with parental responsibility who are involved in the decision, alongside the CYP. When caregivers attend the consenting process, parents/legal guardians will also be seen on their own. Where only one parent/legal guardian attends, the reasons for this will be recorded.

The PI/SI will check again that the possibility of fertility preservation was discussed with each CYP and their wishes to access this prior to GnRHa treatment will be recorded. Fertility preservation options should be discussed at each appointment considering endocrine and other medical options.

Informed consent will be obtained in person on paper from parents/legal guardians and assent from CYP by a PI/SI, following Good Clinical Practice (GCP) guidelines. The CYP and their parents/legal guardians will be specifically encouraged to take as much time as they need to make a decision.

For children, informed assent will include demonstrating understanding, retention, and the ability to weigh up the potential benefits and risks of participation, and to communicate their decision freely and without coercion. Clinicians must document the young person's and parent(s)' understanding of the trial, including direct quotes where possible, and ensure that both individual and joint discussions have taken place.

A standardised checklist—modelled on that used in the national MDT process—will be employed to ensure that all key aspects of the trial, including the nature of the intervention, potential risks (including those not yet known), implications for fertility, and the right to withdraw, have been thoroughly discussed and understood. Any safeguarding concerns, communication barriers, or co-occurring difficulties that may affect the young person's ability to assent or comply with trial procedures will be addressed and documented. Reasonable adjustments should be made where necessary. However, consent from a parent or legal guardian is required for the young person to participate in the research.

### 3.5.2 Informed Consent for HORIZON INTENSIVE

Participants will be recruited in person using paper consent forms. Recruitment may occur at any point during a participant's involvement in the broader PATHWAYS HORIZON study. However, researchers will aim to align recruitment into HORIZON INTENSIVE with the timing of annual assessments to optimise data collection intervals and minimise participant burden. To further reduce burden, the visit during which consent is obtained should ideally coincide with the collection of cognitive and physical health measures. This approach ensures that participants are not required to attend additional visits solely for consent procedures, and that data collection is streamlined.

### 3.5.3 Informed Consent for CONNECT

Informed assent/consent for CONNECT MR imaging will take place at the same time as enrolling in TRIAL or HORIZON INTENSIVE. It will follow the same route as that used for informed assent/consent for the main study, with separate participant information sheets (PIS) and informed assent/consent form.

# 4 Data Collection & Data Entry

## 4.1 Participant Timeline

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Registration form & consent | X | | | | | | | | | | |
| Eligibility | | X | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | |
| BASELINE CHARACTERISTICS # | | | | | | | | | | | |
| ADHD (SNAP-IV) | | X | | | | | | | | | |
| Autism (SCQ) | | X | | | | | | | | | |
| About Yourself Questionnaire | | X | | | | | | | | | |
| Status form | | | X | X | X | X | X | X | X | X | |
| QUESTIONNAIRES ## | | | | | | | | | | | |
| Quality of Life (KIDSCREEN-10) | | X | | X | | X | | X | | X | X### |
| KIDSCREEN-52 – all domains | | X | | X | | X | | X | | X | X### |
| Personal priorities | | X | | | | X | | | | X | X### |
| Gender Identity Questionnaire^^^ | | X | | | | X | | | | X | X### |
| Social Transition Questionnaire | | X | | | | X | | | | X | X### |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Anxiety and depression symptoms (RCADS-25) | | X | X | X | | X | X | X | | X | X### |
| Suicide/ Self Harm (ASQ) | | X | X | X | | X | X | X | | X | X### |
| Gender dysphoria (UGDS-GS) | | X | | | | X | | | | X | X### |
| Body image/ dysphoria (BIS-GS) | | X | | | | X | | | | X | X### |
| Emotional Dysregulation (DERS-18) | | X | | | | X | | | | X | X### |
| Sexual Attraction Questionnaire | | X | | | | X | | | | X | X### |
| Romantic Relations (ALSPAC measure) | | X | | | | X | | | | X | X### |
| Parental support (PAGES) | | X | | | | X | | | | X | X### |
| Trauma (APCTSS) | | X | | | | X | | | | X | X### |
| Emotional & Behavioural Problems (CBCL, YSR) | | X | | | | X | | | | X | X### |
| Eating Problems (SCOFF) | | X | | | | X | | | | X | X### |
| SCANS | | | | | | | | | | | |
| DEXA+ | X | X | | | | X | | | | X | X### |
| Bone Age (X-Ray) | X | X | | | | X^ | | | | X^ | |
| CLINICAL MEASURES | | | | | | | | | | | |
| Tanner Staging** | X | X | | | | X | | | | X | |
| Self-reported Tanner Staging | | X | | | | X | | | | X | |
| Physical examination | X | X | | X | | X | | X | | X | |
| ***Vital signs | X | X | | X | | X | | X | | X | |
| ECG | X | | | | | | | | | | |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Review of systems (history and examination) | | X | | X | | X | | X | | X | |
| (Optional) Body Composition - Tanita Scale | | X | | X | | X | | X | | X | |
| Telephone check-in | | | X | | X | | X | | X | | |
| Safety bloods | X | X | | X | | X | | X | | X | |
| ***Pregnancy test (pocbp)++ | X | X | | X | | X | | X | | X | |
| Urinalysis | X | X | | X | | X | | X | | X | |
| COGNITIVE MEASURES+ | | | | | | | | | | | |
| General Intelligence – WISC V | | X | | | | X | | | | X | |
| Inhibition, shifting, verbal fluency – D-KEFS | | X | | | | X | | | | X | |
| Memory: visual recognition, verbal recall - CHAMP | | X | | | | X | | | | X | |
| Memory validity profile - MVP | | X | | | | X | | | | X | |
| Executive functions at home - BRIEF | | X | | | | X | | | | X | |
| MAGNETIC RESONANCE IMAGING (PATHWAYS CONNECT) ## | | | | | | | | | | | |
| Structural/functional Imaging – s/fMRI | | X | | | | X | | | | X^^ | |
| ONGOING | | | | | | | | | | | |
| ***Adverse events log | | | | | | | | | | | X |
| ***Concomitant medications log | | | | | | | | | | | X |
| Withdrawal visit | | | | | | | | | | | X |
| Withdrawal form | | | | | | | | | | | X |
| PHARMACY | | | | | | | | | | | |

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study medication dispensing/administration | | X | | X | X+++ | X | X+++ | X | X+++ | X | |
| Study medication dosing log | | | | | | | | | | | X |

**Legend**

# Not required if already captured as part of PATHWAYS HORIZON
## At baseline and Month 24 only for HORIZON INTENSIVE participants
* All ongoing forms to be reviewed and updated at each visit
** Tanner staging optional at Months 12, & 24 for immediate GnRHa participants; Month 24 optional for delayed GnRHa participants
***Safety review including vital signs, adverse event reporting, concomitant medication review, pregnancy test (POCBP only) at every injection visit for participants switching to 3-monthly or monthly IMP preparation.

+ Baseline and 24 months only for HORIZON INTENSIVE participants
++ People of child bearing potential only
+++ Dispensing at Months 9,15,21 if changing to 3 monthly preparation
^ Bone age scan at M12 & M24 optional
^^ Visit window for final scan of 6 weeks prior to/following final treatment injection
^^^Gender Identity Questionnaire completed only at baseline for Parents
### Ongoing questionnaires and DEXA scans completed annually during follow up period

***Table 2. Schedule of events***

## 4.2 Visit Windows

Note. Please refer to Appendix A for individual Schedule of Events for the immediate and delayed treatment arms in PATHWAYS TRIAL, PATHWAYS HORIZON INTENSIVE, and PATHWAYS CONNECT.

### 4.2.1 TRIAL

Windows for data collection and drug administration are as follows (as per the Schedule of Events in table 2): month 6 +/- 2 weeks; month 12 +/- 4 weeks; month 18 +/- 6 weeks; month 24 +/- 8 weeks. For visits at month 3,9,15 and 21, visit windows are +/- 2 weeks.

In the event a visit falls outside of the target visit window, the visit should be scheduled as soon as possible and the data entered into the relevant visit. Subsequent visits should follow the original visit schedule. If the visit does not occur within the upper bound of the visit window, the treatment will still be delivered however it will be recorded as a major protocol deviation.

For DEXA and bone age X-Rays, baseline scans must be before the first injection. Thereafter, assessments should be conducted within the window specified for each follow up visit.

### 4.2.2 HORIZON INTENSIVE

Visit windows for HORIZON INTENSIVE will follow the same configuration as TRIAL for comparability.

### 4.2.3 CONNECT

For MRI scans, baseline scans must be undertaken prior to the first injection. For delayed-start participants, this also applies to their scan at midpoint, i.e., before their first injection. Otherwise, scans should be within a four week window either side of the midpoint or endpoint date.

Cognitive assessments will ideally take place on the same date as the baseline, midpoint and endpoint injection but otherwise the windows of four weeks either side apply.

## 4.3 Screening Visit

Screening data will be collected as per the Schedule of Events for the screening visit. Required clinical and safety assessments and scans must be completed within the time period specified prior to randomisation in the Schedule of Events (see table 2 footnotes). Re-screening is permitted if initial screening results are inconclusive or if there are changes in the participant's health status that warrant re-evaluation. Informed assent/ consent for PATHWAYS TRIAL will be taken only after participants have undergone screening for assessment of clinical inclusion/exclusion criteria and fulfilled all items on the NMDT discussion framework checklist. CYP will not be

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

consented if randomisation will occur at 16 years of age. The upper limit of the screening period duration is set at ≤ 12 weeks.

## 4.4 Baseline Visit

Eligibility criteria will be confirmed at the baseline visit. Safety tests must be reviewed by a clinician prior to randomisation taking place. The IMP must be dispensed and administered on the same day of randomisation. Baseline data will be collected as per the Schedule of Events in Table 2.

## 4.5 Month 3, 6, 9, 12, 15, 18, 21 visits

Follow up data will be collected as per the Schedule of Events in Table 2 above for the relevant quarterly visit and ongoing section. At each follow up timepoint, a status form is completed; in the event of a missed visit, the status form must be completed.

## 4.6 Month 24 or end-of-study visit

Month 24 data will be collected as per the Schedule of Events in Table 2 above for the M24 visit and ongoing section. In cases where the participant completes the study to month 24, a withdrawal form should be completed at the final visit to indicate they never withdrew.

At the end of study, 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).

Participants will be invited for longer-term annual follow-up to assess the long-term outcomes of the intervention throughout the study period, described under ‘ongoing’.

## 4.7 Continuing care

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 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.

## 4.8 Withdrawal visit

In the event a participant wishes to stop study medication and withdraw from further data collection, a withdrawal form must be completed. Where possible a withdrawal visit should be scheduled to undertake a final set of outcome assessments.

Participants who withdraw from their allocated treatment will be asked to continue to provide follow up data according to the Schedule of Events in Table 2.

## 4.9 Data Entry

Randomisation of participants will be undertaken as per the Randomisation instructions provided separately to sites.

Source data will be entered in the EDC by authorised site staff, typically within 7 days of data collection by going to www.ctu.co.uk and clicking the link to Medrio EDCs.

A full audit trail of data entry and any subsequent changes will be automatically date and time stamped, alongside information about the user making the entry/changes.

It is the responsibility of the site PI team to ensure all baseline data are collected before a participant is randomised.

Source data worksheets (SDWs) will be supplied to all recruiting sites by the Trial Manager. These will be prepared after the database specification is finalised and database testing is complete.

## 4.10 Pre-randomisation data collection

### 4.10.1 Registration

When the participant has signed consent, the study site staff should register the participant in the Medrio EDC system. Upon registration, the system will assign a unique study PIN, to be used for the participant throughout the study.

### 4.10.2 Eligibility

The clinical national multidisciplinary team (NMDT) will review and confirm documentation for clinical eligibility. All eligibility checks must be completed and a physician must confirm eligibility prior to randomisation.

The CYPGS NMDT plays a crucial role in the decision-making processes for young people accessing gender services. The NMDT reviews comprehensive documentation submitted by clinicians, which includes bio-psychological assessments, education reports, safeguarding reports, and individual impact assessments. The NMDT ensures that all relevant information is considered, including the young person's hopes and expectations, family structure, developmental history, physical and mental health, safeguarding concerns, gender development, sexual orientation, education, peer relationships, and social context. The NMDT's recommendations are based on a holistic assessment framework, taking into account the child's capacity to assent or consent, parental capacity to consent, and the overall impact on the young person's development and wellbeing. The submitting clinician will present the case to the nMDT to aid in their considerations.

The presenting clinician will seek the assent of the CYP and consent of the parent/legal guardian to share with the research team demographic information including: month and year of birth, Gender Service (site), birth-registered sex, presence of neurodevelopmental traits/disorder and Tanner stage. If a CYP is considered inelgible for GnRHa, the reason(s) for this decision will be recorded. This will provide a dataset to characterise core clinical features associated with eligibility. The assent/consent will be recorded in the CYP’s medical notes.

### 4.10.3 Medical History

Relevant medical history must be recorded. This will include: past medical history and medication history. If the participant is taking any medications at baseline, the relevant condition should be recorded in the medical history unless it is prophylactic treatment.

### 4.10.4 Demographics

Relevant demographic information will be collected prior to randomisation including initials, age (date of birth), birth-assigned sex, gender identity, country of birth, and ethnicity. Only initials, date of birth and ethnicity will be entered into the TRIAL and HORIZON INTENSIVE database.

### 4.10.5 Randomisation

Sites must confirm in the EDC system whether TRIAL participants were randomised into the study or not. The randomisation procedure will be provided to sites as part of the set up documentation.

## 4.11 Baseline characteristics

The following measures will be collected for the purposes of baseline characterisation for TRIAL and HORIZON INTENSIVE participants. Baseline characterisation measures will be completed primarily on the Medrio ePRO module (see section 7.1.1.1). Source data worksheets (SDWs) will be provided to recruiting sites for participants to complete self-report measures on paper where required. If the participant has completed these measures as part of PATHWAYS HORIZON, they do not need to be repeated.

### 4.11.1 Swanson, Nolan, and Pelham-IV (SNAP-IV)

The SNAP-IV[22] is an 18-item scale used to assess symptoms of ADHD, across two subscales: inattention and hyperactivity/ impulsivity. Parents/caregivers will be asked to rate how often their child endorses each item on a 4-point Likert scale (0= not at all; 3= very much). We will obtain parent report questionnaires only. Duration 3 minutes.

### 4.11.2 'About Yourself' Questionnaire for Parents/Caregivers

The About Yourself questionnaire is a non-validated 4-item self-report measure for parents. Two questions were designed to evaluate gender identity and sex registered at birth, based on questions from the UK based National LGTB Survey [23]. The Parent will be asked 'Do you identify' as: 'woman', 'man', 'transwoman', 'transman', 'non-binary/genderqueer/agender/gender fluid', 'don't know', 'prefer not to say', 'other'. Parents will next be asked; 'What was your sex assigned at birth?', with response categories of 'female', 'male', and 'prefer not to say'. The 'About Yourself' questionnaire will also assess the parent's relationship to the CYP, with response options 'Biological parent', 'Adoptive parent', 'Step-parent', 'Biological Grandparent', 'Other biological relative', 'Foster carer', 'Other carer/ legal guardian', and the parent's ethnicity. This will be administered at baseline only. Duration: 1 minute.

### 4.11.3 Social Communication Questionnaire (SCQ)

The SCQ[24] is a screening tool used to assess traits of autism spectrum disorder (ASD). The SCQ current version measures symptoms over the previous 3-months.

The measure comprises 40 yes/no questions and will be completed by parents/caregivers only. Total scores range between 0 and 39, and a clinical cut-off of 15 is used to detect probable ASD. Duration: 5 minutes.

## 4.12 Efficacy data

Participant self-report measures should ideally be completed in the absence of the caregiver; in all cases it should be documented in the eCRF whether the caregiver was present. Self-report measures will be completed primarily on the Medrio ePRO module (see section 7.1.1.1). SDWs will be provided to recruiting sites for participants to complete self-report measures on paper where required. Researchers will review responses prior to clinic appointments and discuss with participants any missing measures or items, prompting for completion.

Parent/caregiver informants will be encouraged to complete their parallel questionnaires as close as possible in time to those completed by CYP.

### 4.12.1 PRIMARY OUTCOME - KIDSCREEN-10

The KIDSCREEN-10[25] is a 10-item questionnaire designed to evaluate the subjective health and well-being of CYP using a single factor general health-related quality of life (HRQoL). All 10-items are included within the KIDSCREEN-52. The KIDSCREEN-10 will therefore be administered as part of the KIDSCREEN-52, as described below. Primary outcome scores will be obtained separately, using the single factor structure of the KIDSCREEN-10.

### 4.12.2 Secondary Outcomes

#### *4.12.2.1 KIDSCREEN-52*

The KIDSCREEN-52[25] is a 52-item questionnaire designed to evaluate the subjective health and well-being of CYP. It assesses ten dimensions: physical activities and health, feelings, general mood, about yourself, free time, family and home life, money matters, friends, school and learning, and bullying. Items are scored using a 5-point Likert scale (e.g., 1= not at all; 5= extremely). Higher scores indicate higher health-related quality of life and well-being. Both self-report and parent-report versions will be administered. Duration: 7 minutes.

#### *4.12.2.2 Gender Identity*

The gender identity questionnaire for CYP is a 2-item self-report measure developed for PATHWAYS with the PATHWAYS advisory group. In this measure, gender identity is defined as someone's internal sense of gender. CYP will be asked 'What best describes your gender identity?' to assess their current expression of gender identity. The response options will include 'definitely a boy', mainly a boy', 'definitely a girl', 'mainly a girl', 'neither a boy or girl', 'not sure' and 'none of the above'. CYP over 12 years will additionally be asked about gender identity labels, specifically 'Are there other words that you use to describe your gender identity? (tick all that apply),

'cisgender', transgender', 'non-binary', 'agender', 'genderfluid', 'genderqueer', 'two-spirit' and 'other'. Duration: 1 minute.

#### *4.12.2.3 Social Transition Questionnaire*

The Social Transition Questionnaire is a single-item, self-report measure designed to assess the extent to which participants have socially transitioned across different everyday settings. Social transition refers to changes in the way the CYP lives that align more closely with their experienced gender, including changes to their appearance, clothing, name, pronouns or behaviour, for example. Participants are asked: "Have you socially transitioned in any of the following settings?", followed by a checklist of five settings: Home, School, With Friends, Online, and Any Other Setting (e.g., holiday). For each setting, participants are instructed to select one of three response options: "Most or all the time", "Sometimes", or "Never". This measure has been developed specifically for the PATHWAYS study in consultation with stakeholders and community advisors. Duration: 1 minute

#### *4.12.2.4 Personal Priorities*

CYP and their parents/caregivers will be asked to consider a range of domains of symptoms and everyday functioning/experience and give them relative weights as priority outcomes from their treatment for gender incongruence. This is a novel measure although the method of personal priorities has previously been used in research[26]. The domains included in the personal priority options will be developed based on a systematic review of outcome domains in gender incongruence research, information previously provided by focus groups of CYP with gender incongruence and their parents and the PATHWAYS ENGAGEMENT advisory boards.

#### *4.12.2.5 Adolescent Primary Care Traumatic Stress Scale (APCTSS)*

The APCTSS[27] is a 5-item measure of DSM-5 symptoms of PTSD. The participant is asked whether they have experienced each of the five symptoms within the past month, with a Yes/No response. Total scores range from 0-5, with a score of 2 or more being indicative of probable PTSD. A non-validated parent report version has been designed to be a direct comparison of the CYP self-report. Duration: 2 minutes.

#### *4.12.2.6 Revised Child Anxiety and Depression Scale (RCADS)*

The RCADS-25[28] is a 25-item measure used to assess symptoms of anxiety and depression in CYP. Each item is rated using a 4-point Likert scale (0= never; 3=always), with total scores ranging 0-45 on the anxiety subscale and 0-30 on the depression subscale. CYP self-report (RCADS-C-25) and parent-report (RCADS-P-25) versions will be administered. The parent-report measure has been adapted to include gender neutral language. Duration: 5 minutes.

#### *4.12.2.7 Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR)*

The CBCL[29] is a 113 item scale designed to measure behavioural and emotional functioning in CYP, across two broad dimensions, internalising and externalising

problems. Each item is rated using a 3-point Likert scale (0= not true; 2= very true or often true). Parent-report questionnaires (CBCL) and Youth Self-Report (YSR) questionnaires will be obtained. Validated versions of the measures which include gender neutral language will be administered. Duration: 15 minutes.

#### *4.12.2.8 Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS)*

The UGDS-GS[30] is an 18-item questionnaire that measures gender dysphoria i.e. distress relating from the incongruence between an individual's birth registered sex and their gender identity, and gender affirmation i.e. comfort from living in accordance with their gender identity. Respondents are asked to rate each item using a 5-point Likert scale (1= disagree completely; 5= agree completely). Total scores range from 0-90, with higher scores indicating higher gender related distress. Only CYP self-report versions will be obtained. Duration: 3 minutes

#### *4.12.2.9 Body Image Scale – Gender Spectrum (BIS-GS)*

The BIS-GS[31] is a gender-neutral version of the Body Image Scale (BIS)[32] used to assess an individual's relationship with their body. The scale consists of 33 items. The format of the measure has been adapted such that participants are asked to indicate whether they 'Have? each body-part (e.g. vagina) with a yes/no response, as opposed to whether they 'Don't Have?' each body-part. Respondents subsequently rate their feelings towards the body parts that they do have, and their feelings towards not having the body parts that they don't have using a 5-point Likert scale (1= very satisfied; 5= very dissatisfied). Respondents also rate whether they would want to change each body part if it was possible through medical or surgical treatment using a yes/no response. Higher scores indicate greater body dissatisfaction. Only CYP self-report versions will be obtained. Duration: 3 minutes.

#### *4.12.2.10 Ask Suicide-Screening Questions (ASQ)*

The ASQ[33] is a brief 4-item instrument used to assess risk of suicide; including suicidal ideation, history of suicide attempt and burdensomeness factors. Each item is answered using a "yes" or "no" response, with total scores ranging from 0 to 4. A non-validated parent report version has been designed to be a direct comparison of the CYP self-report. The wording of question 4 will be altered at follow-up to assess whether the CYP has attempted suicide in the past year (i.e. since the previous time-point of data collection). Duration: 1 minute.

#### *4.12.2.11 SCOFF Questionnaire*

The SCOFF[34] is a 5-item screening tool designed to identify the core symptoms of anorexia nervosa or bulimia nervosa. Each item is scored 0= "no" or 1= "yes". Total scores range from 0 to 5, with higher scores indicating more disordered eating behaviour and a score of 2 or more considered likely indicative of an eating disorder. A non-validated parent report version has been designed to be a direct comparison of the CYP self-report. CYP self-report and parent-report versions will be obtained. Duration: 1 minute.

#### *4.12.2.12 Difficulties in Emotion Regulation Scale (DERS)*

CYP will complete the short version of the Difficulties in Emotion Regulation Scale (DERS-18)[35], which consists of 18 self-report items measuring emotional difficulties. The DERS-18 generates scores across six subscales: nonacceptance of one's emotions, lack of goal-directed behaviour during negative emotions, impulse control during negative emotions, emotional awareness, access to emotion regulation strategies and emotional clarity[35]. The 29-item DERS-P will be administered to parents/caregivers. The DERS-P generates scores across four subscales: catastrophise, negative secondary, attuned and distracted. Each item is scored using a 5-point Likert scale (1= almost never; 5= almost always) such that higher scores indicate greater difficulties in emotion regulation. The parent measure has been adapted to include gender neutral language. Duration: 4 minutes.

#### *4.12.2.13 Sexual Attraction*

A questionnaire including one question 'Who are you attracted to?', with the response options, 'Prefer not to say', 'Males', 'Females', 'Males and females', 'Neither', 'Not sure' was designed to measure sexual attraction. Only self-report questionnaires will be obtained from young people aged 12 years and older. Duration: 1 minute.

#### *4.12.2.14 Romantic Relations*

Young people aged 12 and above will complete the ALSPAC Romantic Relations measure[36], which assesses whether young people have engaged in any of the 14 sexual behaviours from the Adolescent Sexual Activities Index (ASAI)[37], and the sex of the person with whom they did. Items are scored 0= they have not engaged in that sexual activity, 1= they engaged in that sexual activity with the other sex, 2= they engaged in that sexual activity with both sexes, 3= they engaged in that sexual activity with the same sex. Duration: 3 minutes.

#### *4.12.2.15 Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES)*

The PAGES-Y[38] is a 14-item self-report measure used to assess CYP's experience of parental acceptance of gender identity/ expression. The measure includes two subscales, perceived parental non-affirmation and perceived parental acceptance. CYP will rate each item based on their overall experience of support from both parents/caregivers within a single measure, as opposed to providing individual scores for each parent/caregiver. The PAGES-P[39] is a 16-item parent-report version measuring parental acceptance and support. Each item is responded to using a 5-point Likert scale (1= strongly disagree; 5= strongly agree), with higher overall scores indicative of greater perceived parental support. Duration: 3 minutes.

## 4.13 Cognitive Assessments

### 4.13.1 Wechsler Intelligence Scale for Children (WISC-V)

The WISC-V[40] is a robust and highly reliable cognitive assessment used to evaluate a child's intellectual functioning. We will administer the 10 primary subtests only to obtain 5 composite scores: Verbal Comprehension (Similarities, Vocabulary), Visual Spatial (Block Design, Visual Puzzles), Fluid Reasoning (Matrix Reasoning, Figure Weights), Working Memory (Digit Span, Picture Span), Processing Speed (Coding, Symbol Search). The WISC-V is administered and scored on tablets digitally using the Pearson Clinical Q-Interactive platform. Duration: 60 minutes.

### 4.13.2 Delis-Kaplan Executive Function System (D-KEFS)

The D-KEFS[41] is a set of subtests used to assess key components of verbal and non-verbal executive function in children and adults, including flexible thinking, inhibition, problem solving, planning, impulse control, concept formation, abstract thinking, and creativity in both verbal and spatial modalities. We will administer three of the D-KEFS subtests including the verbal-fluency test, colour-word interference test and sorting test. The D-KEFS is administered in a game-like, engaging format in which the researcher provides instructions and feedback throughout. The D-KEFS subtests are administered and scored on a mixture of Q-Interactive and paper. Duration: 30 minutes.

### 4.13.3 Child and Adolescent Memory Profile (CHAMP)

The CHAMP[42] is a measure of learning and memory administered among children and adolescents aged 5-21. The CHAMP includes four subtests; verbal memory, visual memory, immediate memory and delayed memory. Subtest scores combine to yield an overall Total Memory Index, with higher scores indicative of better memory performance. The CHAMP is administered and scored on paper. Duration: 35 minutes.

### 4.13.4 Memory Validity Profile (MVP)

The MVP[43] assesses whether a CYP's memory score is a valid estimate of their memory ability. This individually administered test is designed for CYP aged 5-21 and includes two subtests: visual and verbal. The MVP visual and verbal subtest scores combine to yield an MVP Total score, with higher scores indicating greater likelihood of invalid performance. The MVP is administered digitally and scored on paper. Duration: 6 minutes.

### 4.13.5 Behaviour Rating Inventory of Executive Function (BRIEF)

The BRIEF2[44, 45] is the second edition of the BRIEF[45] and is a 63-item parent-reported measure designed to assess executive function in CYP aged 5-18. Each item is scored using a 3-point Likert scale (1= never; 3= often). The BRIEF2 provides 3 index scores: a Behavioural Regulation Index (combining the subscales Inhibit and Self-Monitor), an Emotion Regulation Index (combining the subscales Shift and

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

Emotional Control), a Cognitive Regulation Index (combining the subscales Initiate, Working Memory, Plan/Organize, Task-Monitor and Organisation of Materials), and a Global Executive Composite score (combining all 9 subscales). The BRIEF is administered and scored on paper. Duration: 10 minutes.

## 4.14 Safety Data

### 4.14.1 Physical Exam

The physical examination will be the standard exam conducted by a qualified physician at screening and repeated at baseline if 3 months has elapsed. The extent of subsequent examinations will be at the discretion of the physician, as clinically indicated. The physician will be adequately experienced and delegated by the PI to undertake Tanner staging assessments. A chaperone will be present throughout any physical examination. Any examinations not required should be recorded as 'not done'.

The physical assessment may include:

- Paediatric physical examination of cardiovascular system, respiratory system and abdomen for general health.
- Height and weight will be recorded.
- Optional body composition assessment using Tanita scales may be used to obtain detailed body mass percentages.
- Routine nursing observations including heart rate, blood pressure, respiratory rate and oxygen saturations

Height should be measured using a stadiometer to the nearest millimetre. Weight should be measured using calibrated scales with the participant in light clothing. If a young person prefers to remain more covered due to body-related distress, this should be noted and considered when interpreting the measurement.

### 4.14.2 Electrocardiogram (ECG)

A 12-lead ECG will be collected at screening for systemic cardiac monitoring. ECGs will be collected at follow up visits where indicated clinically.

### 4.14.3 Puberty Staging Assessment (Tanner staging) – Clinical Examination

Tanner staging assessments will be conducted at screening for all TRIAL participants by a qualified, adequately experienced physician, delegated by the PI at each site. For both TRIAL arms, if more than 3 months out of date at the baseline visit, the Tanner staging assessment will be repeated. For immediate group participants, the 12 and 24 month assessments are optional. For those in the delayed start GnRHa arm, there will be a further Tanner stage assessment at 12 months, prior to initiation of intervention – the 24 month assessment is optional. A chaperone will be present throughout the Tanner staging assessment. Chaperones cannot be the CYP's accompanying parent/legal guardian.

### 4.14.4 Puberty Staging Assessment – Self-Reported

CYP will be presented with a sex-specific pubertal self-assessment questionnaire which includes realistic coloured images[46] from which they are asked to select the picture that they believe most accurately represents their current stage of pubertal development. 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.

Pubertal self-assessment questionnaires completed by TRIAL participants at the baseline, month 12 and month 24 visits. PATHWAYS HORIZON INTENSIVE participants will complete pubertal self-assessment questionnaires at baseline and 24 months.

### 4.14.5 Vital Signs

Systolic and diastolic blood pressure, weight, height, and BMI centile will be obtained at each visit. Vital signs will be measured in upright position after the participant has been rested for five minutes.

### 4.14.6 Dual X-Ray Absorptiometry (DEXA) Scan

Hip and spine DEXA Scans will be performed, with the option of whole-body and/or volumetric DEXA scans solely for clinical reasons where deemed clinically indicated by the PI or SI. DEXA scans will be performed at screening, month 12 and month 24 for all TRIAL participants. For HORIZON INTENSIVE, DEXA scans will be performed at baseline and month 24 only.

DEXA scans will assess bone mineral density (BMD); absolute BMD ($g/cm^2$) and age and birth-registered sex standardised Z-scores calculated by machine software will be reported. Scans should be performed on the same scanner and analysed with the same software version throughout the trial. If software changes locally at endocrine centres, preceding scans should be re-run with the new software. In the event the DEXA scanner breaks during the trial, subsequent scans should ideally be taken on a scanner by the same manufacturer.

### 4.14.7 Bone Age X-Ray

Bone age X-Rays of the left hand/wrist will be performed at screening for all TRIAL participants. Bone age X-Rays will be reported using the Tanner Whitehouse II method. For TRIAL participants the month 12 and 24 scans are optional - bone age X-Rays do not need to be repeated if growth plates are fused. An initial bone age assessment will allow calculation of expected final height and comparison to actual final height can be made. For HORIZON INTENSIVE participants, bone age X-Rays will be performed at baseline only.

### 4.14.8 Adverse Events

During each visit, participants will be asked about adverse events. All adverse events will be recorded in an ongoing adverse event log. Recording of symptom changes is only necessary when treatment is initiated or when the clinician identifies an unusual rate of change. In the immediate arm, there will be an additional telephone visit led by Clinical Nurse Specialists (CNS) or a delegated medical professional, at 3 and 15 months to ask about adverse events that may require discussion with the PI or SI. A researcher will conduct the telephone visits at 9 and 21 months. Within the delayed arm, there will be a parallel researcher-led telephone visit at 3, 9 and 21 months, with a telephone visit at 15 months led by a CNS or delegated medical professional. All telephone check-ins will follow a standardised proforma with clear guidance on escalation to clinical staff if any concerns arise. This ensures consistency in data collection and participant safety, while allowing flexibility in staffing.

The measures included at each assessment point will assess several adverse events (AE) experienced since the last assessment. Systematic enquiry will include, for birth-registered females, breakthrough menstrual bleeding. All participants will be asked about severe and persistent headaches, galactorrhoea, significant weight changes, unexplained pain, persistent nausea or vomiting, and any other physical symptoms that significantly impact the participant's daily functioning. These physical events will be assessed for their severity and potential relation to the study intervention, and appropriate medical interventions will be provided as necessary.

Follow ups will include suicidal thoughts, suicidal behaviour, a marked increase in the severity of anxiety or depression symptoms, defined as T-score on RCADS subscales >80 when previously lower, increased mental distress requiring unplanned clinical appointments and/or A&E attendances. They will also include detailed information on the child's height and weight, prescribed medications, new diagnoses (both neurodevelopmental and mental health, as well as physical health), and the number of GP appointments attended in the past year. It will also cover any planned surgeries or procedures, A&E visits, reasons for these visits, and whether they led to overnight admissions.

Any hospital admission for an overnight stay will be recorded as a serious adverse event (SAE).

### 4.14.9 Concomitant Medications

During each visit, participants will be asked about their current medication, including private prescriptions, over-the-counter medications and supplements. All concomitant medication will be recorded in an ongoing concomitant medication log.

### 4.14.10 Withdrawal

A withdrawal form must be completed in the event of participant death or where the participant has stopped taking study medication and is no longer prepared to provide

any follow up data or have their caregiver or family doctor provide any follow up data. Where the participant has stopped study intervention but is still being followed for primary outcome data, a withdrawal form should not be completed, but a status update must be recorded in the EDC at each subsequent visit.

Participants who stop the IMP will be followed up for outcomes where possible.

## 4.15 Laboratory Data

All tests listed below will be performed as per the time points indicated in the schedule of events in Table 2 (section 4.1). In addition, laboratory safety tests may be performed at unscheduled times, if deemed necessary by the PI and abnormal results recorded as an adverse event if clinically significant. Standard local NHS laboratories will be used to perform the tests at each trial site. If samples are requested elsewhere (eg via a community based doctor) the laboratory results report should be requested. Results must be printed and retained with the source data worksheets, after being reviewed and signed by a physician. Where the results indicate an adverse event or medical condition, this should be recorded in the medical history (at baseline) or on the adverse event log if occurring after randomisation.

Clinically significant abnormalities will be reported to the clinical team and discussed with the participant as necessary, as well as being recorded in the medical history form at screening and baseline or the adverse event form post-randomisation.

Individual result values will not be transcribed to the EDC system unless outside the normal range.

### 4.15.1 Safety Bloods

#### *4.15.1.1 TRIAL Participants*

SCREENING AND BASELINE

All blood tests detailed below will be required at screening and baseline. A serum beta HCG will only be required at baseline to exclude early pregnancy prior to initiation of GnRHa.

Baseline blood tests will usually require anyone on contraceptive treatment (and other hormones as indicated) to have a washout period – where the hormones are not taken – prior to the blood test to ensure true basal hormone panel blood results are interpreted accurately. This will be a clinical decision that takes account of risk of becoming pregnant (and will consider the potential to move to other forms of contraception). The length of washout period is dependent on the type of medication the CYP is using and there may be some circumstances where a washout period is not required. The baseline blood test may need repeating if the washout period needs to be extended to show gonadal axis function. The length of washout period is

to be discussed with and determined by the expert endocrine panel. This panel consists of experienced paediatric endocrinologists from the UK and EU.

Screening blood tests do not require a washout period. Blood tests are to be repeated at the baseline visit if more than 3 months has elapsed since screening.

FOLLOW UP VISITS

At 6-monthly follow-up visits, the following blood tests are mandated: FSH, LH, Oestradiol, Testosterone, Renal Profile, Full Blood Count, Magnesium, Prolactin, Lipid and Bone Profiles. Additional blood tests may be ordered by the PI or SI where clinically indicated. These may include tests outside the standard panel, based on individual participant needs or emerging safety concerns.

HAEMATOLOGY

**FULL BLOOD COUNT:**

Haemoglobin Platelet count Total and differential leukocyte count (neutrophils, lymphocytes, monocytes, eosinophils, basophils.) Haematocrit Red blood cell count

BIOCHEMISTRY

**RENAL PROFILE:**

Sodium Potassium Creatinine Urea

**LIVER PROFILE:**

Alanine Transaminase (ALT) Aspartate Aminotranferase (AST) Alkaline Phosphatase (ALP) Bilirubin Albumin Total Protein

**LIPID PROFILE:**

Total Cholesterol HDL LDL

**BONE PROFILE:**

Calcium Phosphate Parathyroid Hormone (PTH)

**OTHER:**

Ferritin Follicle Stimulating Hormone (FSH) Luteinising Hormone (LH) Oestradiol Testosterone Prolactin Thyroid Stimulating Hormone Free T4 Vitamin D

#### *4.15.1.2 HORIZON INTENSIVE Participants*

HORIZON INTENSIVE participants will complete the same blood tests as TRIAL participants at baseline and month 24.

### 4.15.2 Pregnancy Tests

Pregnancy tests will only be conducted in TRIAL participants of child-bearing potential.

**SERUM PREGNANCY TEST:**

Serum beta-hCG will be determined for birth-registered female study participants of child-bearing potential prior to dosing. Serum testing is mandated at screening and baseline. Thereafter urine pregnancy testing is permitted but if not available, serum testing is acceptable.

**URINE PREGNANCY TEST:**

Urinary pregnancy testing will be required at screening and follow-up visits.

At baseline, if the delay waiting for serum pregnancy test results will make randomisation impossible, a urine beta-hCG pregnancy test may be used in addition to (not instead of) the serum pregnancy test to allow the site pharmacy adequate time post-randomisation to prepare the study medication for dispensing on the same day.

### 4.15.3 Urinalysis

Urinalysis will be performed at baseline and follow-up visits and is required for monitoring of potential rare side-effects of GnRHa. Part of the urinalysis is to monitor participants' glucose level as diabetes is a potential side effect of the medication.

| | |
|---|---|
| Ketones | Urobilinogen |
| Bilirubin | Leukocyte esterases |
| Protein | Blood |
| Glucose | Nitrite |

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

## 4.16 Injection Visit Safety Data Collection

As per the schedule of events (table 2), if participants are switched to alternative IMPs with 3-monthly or monthly administration, a brief safety visit will be conducted at each study medication administration visit, including the following reviews as a minimum:

- Vital signs
- Adverse event reporting
- Concomitant medication review
- Pregnancy test (POCBP only)

## 4.17 Magnetic Resonance Imaging Data

Participants consenting to take part in PATHWAYS CONNECT will undergo structural and functional MRI imaging (sMRI/fMRI) at baseline, month 12 and month 24 as per the Schedule of Events. HORIZON INTENSIVE participants will be scanned at baseline and 24 months only. The final scanning window will be 6 weeks before/after the final treatment administration.

### 4.17.1 MRI Imaging Protocol

Prior to the scan, the radiographer will screen the participant for any contra-indications for MRI scanning such as metallic implants or devices using an established institutional procedure. We will have a range of options to try to make the MRI experience as pleasant as possible. Depending on the availability of equipment and participant preferences this may include for example, a mock scanner (a non-operational MRI scanner) to familiarize the participant with the scanning procedure; an interactive virtual reality (VR) setting while scanning. The VR system allows participants to interact with visual content using their eyes using a pair of MR-conditional cameras in the scanner. The eye video recordings can also be used to estimate their gaze (what they are looking at on the screen) but will not be recorded. The VR system can also be used to present stimuli that can be used to identify the associated patterns of brain activity. This should improve the success rates of acquiring good-quality images. There may be instances where the VR system has unforeseen technical failures, in which case we will still conduct the scan.

Guidance will be given to participants on how they can contact the radiographer using a buzzer and microphone throughout the scan in case they need to stop the scan or communicate any other relevant information. All participants will have hearing protection applied prior to scanning in the form of mouldable silicon earplugs and cushioned headphones. The total MRI scanning will take no more than 90 minutes (including set-up and allowing for breaks), with approximately 40-60 minutes of scan time, however, we aim to complete the scan within shorter time frames if possible.

MRI sequences will include (1) structural/anatomical imaging including T1, T2 and T2* weighted images (2) diffusion-weighted imaging (uses the diffusion of water molecules to inform on tissue microstructure), (3) functional imaging (uses changes in blood oxygenation to inform on brain activity), (4) magnetic resonance spectroscopy (uses frequency information to inform on metabolite content, such as levels of NAA, Cr, Cho, glutamate, GABA, Glx & GSH), and (5) perfusion/susceptibility-weighted imaging (to inform on blood flow and content). Other acquisition sequences may be added if indicated, however the total time being scanned will not exceed 60 minutes. Any modified/customized acquisition sequences will adhere to the manufacturer's safety specifications and will be reviewed and authorized by the local MRI safety committee.

#### *4.17.1.1 Incidental Findings*

In the case of clinically significant incidental findings on MRI scan, the neuroradiology team will contact the participant's GP and the study team who will communicate with the family for further consultation/investigation if needed. Where it is deemed necessary, the participant's local Gender Service and paediatric team will also be informed. In this case, the report will be shared confidentially with designated individuals in the study team to facilitate communication with the family.

## 4.18 IMP Dosing Data

### 4.18.1 Study Medication Dispensing and Dosing Log

Study medication dispensing and dosing, including the IMP preparation being administered, or any active temporary or permanent discontinuation of study medication will be recorded on the study medication dispensing and dosing logs and stored in the site Pharmacy Files.

## 4.19 Measures to promote participant retention

To promote participant retention, the following measures will be implemented:

- Regular follow-up appointments with reminders sent via phone, email, or text message.
- Providing reimbursement for travel and expenses to participants and their parents/guardians
- Providing vouchers for completing outcome measures:
  - £30 for each cognitive assessment
  - £15 for each MRI scan.
  - HORIZON INTENSIVE participants will receive £15 for completion of DEXA scans and bloods
- Offering flexible scheduling for appointments to accommodate participants' availability.
- Ensuring a supportive and engaging environment during study visits.

# 5 Interventions

## 5.1 Explanation for the choice of comparators

The trial will compare immediate vs. delayed start (1 year) of GnRHa.

## 5.2 Intervention and comparator description, dosing and labelling and intervention

### 5.2.1 Medication:

The primary intervention all participants will initiate treatment on is Decapeptyl® SR (long-acting formulation of Triptorelin) 22.5mg intramuscular injection (6 monthly preparation).

### 5.2.2 Labelling:

The information presented on the IMP labels will be annex 13 compliant.

### 5.2.3 Administration:

The dose of Decapeptyl SR (long-acting formulation of Triptorelin) 22.5mg is administered every six months at 0, 6, 12, 18, and 24 months post-randomisation. This dosing regimen is in adherence to the approved schedule in the Decapeptyl SmPC for the indication of precocious puberty in the same age group, used in routine clinical care. In cases of documented tolerability issues, inadequate suppression of puberty, or product unavailability, alternative regimens may be implemented in accordance with expert panel recommendation and confirmation, as outlined in Appendix C with the following products:

- Decapeptyl® SR (long-acting formulation of Triptorelin) 11.25mg intramuscular injection (3 monthly preparation)
- Prostap 3 DCS (Leuprorelin Acetate) 11.25mg intramuscular injection (3 monthly preparation)
- Gonapeptyl (Triptorelin) 3.75mg intramuscular injection (1 monthly preparation)

### 5.2.4 Monitoring:

Following administration, participants will be monitored during their clinic visit for any immediate adverse reactions post-injection. The length of the monitoring period is determined by the principal or sub-investigator at the endocrine centre based on their clinical expertise.

Regular follow-up appointments to assess efficacy and safety, including monitoring hormone levels and physical development.

Routine blood tests, DEXA scans, and physical assessments (height, weight, BMI, blood pressure, body composition using Tanita scales if available, and puberty staging).

Psychosocial screening to identify any unmet needs and escalate these to appropriate services.

### 5.2.5 Fertility Preservation:

Discussion of fertility preservation options with referrals to fertility specialists if desired.

### 5.2.6 Comparator:

**Delayed Start:** Participants in the delayed start group will begin GnRHa treatment one year after randomisation. They will receive the same monitoring and assessments as the immediate start group.

## 5.3 IMP accountability

The Clinical Trials Pharmacy teams at recruiting sites will maintain records of medication dispensing and dosing.

Participants will be monitored for adherence to the injection schedule.

## 5.4 IMP Storage

GnRHa injections will be stored according to the SmPC. The clinical trial pharmacy team will ensure proper storage and handling of the medication as delegated by the PI.

## 5.5 Returns & Destruction

A record of study drug returns is not required as the intervention is administered in clinic as a single dose at each visit. IMP components should be disposed of in adherence to the Trust's pharmaceutical waste management procedures.

Any medicinal product not administered immediately following reconstitution for injection should be disposed of in accordance with local procedures and documented on the accountability log as not administered.

In the event the IMP is dispensed and not administered prior to re-constitution of the component parts, this should be documented on the master accountability log and the IMP may be re-dispensed.

## 5.6 Discontinuing allocated interventions

Participants may discontinue GnRHa treatment at any time without any detrimental impact on their care. Reasons for discontinuation will be documented, and participants will remain in follow-up according to their randomised arm's schedule of events until the end of the study .

Health care team-initiated discontinuation criteria include:

- Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient, including serious or intolerable AE that prevents the subject from continuing with study participation

- Change in compliance with any inclusion or exclusion criterion that is clinically relevant and affects subject safety, as determined by the Investigator.
- Use of prohibited concomitant medications
- QTc > 470ms
- Pregnancy

When the health care team are considering discontinuation, they will discuss the reasons for this with the participant and their parents/ legal guardians, taking account of their preferences and possible alternative treatment regimes.

## 5.7 Concomitant medications permitted or prohibited during the trial

### 5.7.1 Permitted Medications

Participants may continue to take other medications as prescribed by their healthcare providers.

Any changes in medication will be documented and monitored for potential interactions with GnRHa.

Medications known to affect pituitary gland function or increase prolactin levels (e.g. risperidone) should not be prescribed concomitantly. This includes certain antipsychotics (e.g. risperidone) and metoclopramide. Where such medications are clinically indicated, the potential risks but should be carefully considered. If no suitable alternatives are available, additional monitoring is required.

### 5.7.2 Prohibited medications

Gender affirming hormones are prohibited for participants in this study.

Prolonged use of medicinal products associated with clinically relevant bone mineral density loss, such as systemic glucocorticoids (for >14 days) and traditional anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, valproic acid).

Use of puberty blockers outside this clinical trial.

Any other investigational medicinal products (IMPs).

Drugs known known to prolong QT interval, specifically: IA antiarrhythmics (e.g. quinidine, disopyramide), class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide), and methadone.

### 5.7.3 Non-prohibited Concomitant Potentially QT-Prolonging Drug Risk Management Algorithm

Including but not limited to – moxifloxacin, selective serotonin reuptake inhibitors (SSRIs), Tricyclic antidepressants, and antipsychotic agents.

Objective:

To minimise the risk of QT interval prolongation and Torsade de Pointes in participants receiving GnRHa therapy.

Step 1: Baseline Risk Assessment

Review participant's medication list for known non prohibited QT-prolonging drugs (e.g., SSRIs, antipsychotics).

Assess personal/family history of:

- Congenital long QT syndrome (LQTS)
- Unexplained syncope or sudden cardiac death

Step 2: Risk Stratification

Low Risk: No QT-prolonging drugs, no cardiac history.

Moderate Risk: Single QT-prolonging drug.

High Risk: ≥2 QT-prolonging drugs, congenital LQTS, Family history

Step 3: Management Actions

Low Risk:

- Proceed with only baseline ECG unless symptoms develop.

Moderate Risk:

- ECG at baseline and after dose initiation.
- Avoid adding further QT-prolonging drugs.

High Risk:

- Obtain cardiology review before enrolment.
- QTcF ≥470 ms or cardiologist advises against, exclude participant.
- ECG confirmation and after every administration.

Step 4: Ongoing Monitoring

Repeat ECG only if:

- QT-prolonging drug added
- Symptoms (syncope, palpitations) occur
- Investigator deems clinically indicated

Step 5: Discontinuation Criteria

• Confirmed QTcF >470 ms OR cardiologist opinion of clinically significant risk.

# 6 Assignment of Interventions

## 6.1 Randomisation method

The method of allocation sequence is minimisation.

Participants will be randomized individually in a 1:1 ratio to immediate vs. delayed start of GnRHa. Participants will be minimised based on four stratifying factors. These are birth registered sex (Male/Female), Tanner stage at entry (stage 2/3, stage 4/5), a diagnosis of a neurodevelopmental disorder or high levels of traits (yes/no) and site (7 levels). There will be an initial burn in of 10 participants who are simply randomised to provide an initial imbalance, where the minimisation can then work from. This means the initial participants are allocated to arms, irrespective of their stratifying factors.

## 6.2 Randomisation implementation

### Allocation sequence generation

The randomisation sequence will be generated dynamically by the KCTU team via the KCTU web-based randomisation system, in accordance with the specification agreed with the CI and Senior Statistician. The Chief Investigator, Senior Statistician and TMG will be blinded to the sequence generation.

### Enrolment of participants

Participants will be enrolled in the study for the purpose of CONSORT reporting at the point of signing a consent form to being screened for eligibility and will be part of the target N=226 at the point of randomisation.

### Assignment of participants to interventions

Recruiting sites will assign participants to interventions by logging into the 'KCTU randomisation system' at www.ctu.co.uk (click 'randomisation' and select 'PATHWAYS study) and entering the participant's year of birth and age and stratifiers. The system will randomise the participants to active immediate or delayed in a ratio of 1:1.

### Randomisation procedure

The Randomisation procedure will be provided in the site set up documentation.

## 6.3 Blinding status of researchers

| Individual blinding status | Blinded | Unblinded |
|---|---|---|
| Chief Investigators | X | |
| Principal Investigators and all other staff at site | | X |
| Co-applicants | X | |
| Trial Managers | | X |

| | | |
|---|---|---|
| Senior Trial Statistician | X | |
| Trial Statistician | | X |
| Pharmacists at site | | X |
| Outcome Assessors/Research Nurses | | X |
| Treating clinicians | | X |
| Programme Steering Committee (TSC) | X | |
| Data Monitoring Committee (DMC) | | X |

**Table 3** - blinding status of PATHWAYS researchers

The blinding status of the research team is detailed in Table 3 above. Trial statistician will be initially blinded to complete the Statistical Analysis Plan, then will be unblinded to complete DMC reports.

*For roles not listed please refer to study delegation logs.

# 7 Data Management

## 7.1 Data Handling and Management

There are three datasets in PATHWAYS TRIAL: the Medrio EDC system dataset (including the Medrio ePRO dataset), the KCTU randomisation dataset, and the Q-Interactive dataset. A separate Medrio EDC Database will be developed for HORIZON INTENSIVE. The CI will act as custodian for all trial data.

Participant data will be pseudonymised using a study PIN generated by Medrio when a participant is registered on the system. All pseudonymised data will be stored on a password protected computer. Access to data held on electronic systems during the trial is restricted to delegated users at recruiting sites and key central staff including the Trial Manager(s), Clinical Research Associate, and Junior Statistician.

Physical source data, including signed consent forms, test results and other medical records should be filed at recruiting sites with the ISF, held in a secure location only accessible to delegated staff. The location of any physical personal data will be documented in the ISF and TMF.

Data Management Plans will be documented in the TMF, detailing relevant security information about the data system.

All essential documents will be archived in the TMF for 25 years following primary publication. Anonymised electronic research data will be backed up on an encrypted hard drive and stored in the TMF for archiving. As per GCP guidelines, identifiable research data will be archived in the ISF for a retention period of 25 years.

All data will be handled in accordance with the Data Protection Act (2018).All trial data will be stored in line with the Medicines for Human Use (Clinical Trials)

Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

Please refer to Appendix B for information on the flow of data throughout the current protocol.

### 7.1.1 Medrio EDC

A web based electronic data capture (EDC) system will be created in collaboration with the CI and trial analyst(s), using the Medrio system. This will be maintained by the King's Clinical Trials Unit (KCTU) and Medrio for the duration of the project. It will be hosted on secure servers by Medrio in the EU.

The CI or delegate (e.g., Trial Manager) will request email usernames and passwords from KCTU for new staff members joining the study and will request access removal when staff members leave the project. EDC access is strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised access the EDC.

Site staff experiencing issues with the EDC system should contact the CI or delegate (e.g., Trial Manager). Medrio training videos are available at www.ctu.co.uk under 'Resources – Events & Training' tab.

Laboratory results may be reviewed directly in hospital laboratory systems where appropriate and need not be transcribed in full to the source data work. Any abnormal results must be recorded and transcribed in the EDC system as an adverse event. Normal results need not be transcribed.

The TM will provide Source Data Worksheets (SDWs) to recruiting sites following completion of database testing. Participating Sites will complete source data location lists defining the source data at their site.

#### *7.1.1.1 Medrio ePRO*

The web based Medrio EDC system will include ePRO (electronic Patient Reported Outcomes).

It is the responsibility of the site staff to ensure ePRO forms are complete at each timepoint for all participants (including where completion is In-Clinic, Remote or on Paper), as a high amount of missing data can render the study uninterpretable.

Authorised staff can check ePRO form completion by logging into their Medrio EDC account. Site staff will be responsible for following up participants who have not completed their ePRO forms before the end of each scheduled timepoint.

Where a participant wishes to withdraw from all further data collection for the study, staff should complete the EDC withdrawal form as soon as possible (i.e., on the

same day) to ensure the participant does not receive further notifications via the automatic ePRO scheduler.

No data will be entered via ePRO unless a participant has signed a consent form to participate in the trial.

The email address and/or telephone number may be entered into the Medrio ePRO system for completion of PROMs and data completion reminders, however as Protected Health Information (PHI) it will only be visible to necessary Medrio users as part of study operations, will be masked from those who do not require access to them, and will not form part of exported datasets.

There are 3 options for ePRO data entry described below:

**1. In Clinic Data Entry by Participant:**

After participant registration in the EDC, authorised staff can launch the relevant ePRO form(s) on a computer/smartphone/tablet and hand this to the participant for completion at the clinic visit.

**2. Remote Data Entry by Participant (e.g., at home completion):**

For 'Remote' ePRO (e.g., completion on a computer/smartphone/tablet at home), when the participant is registered in the EDC and their email address is entered by the authorised staff member, the participant will receive a 'Set Up Profile' notification email. The participant can follow the link in the email to set up their Medrio Profile and create a password.

A notification containing a link to the required ePRO form(s) will be sent to participants as per the pre-defined schedule. The participant will log in to their Medrio Profile, using their email address and password, to complete the active ePRO form(s) for that timepoint.

**3. Data Entry by Site Staff if collected on Paper first:**

If any ePRO forms are completed on paper instead, data entry users will transcribe these data into the EDC (as with any other non-ePRO forms) as soon as possible.

Paper ePRO forms used to transcribe into the EDC should be filed securely as source data in the Investigator Site File (ISF).

### 7.1.2 KCTU Randomisation System

A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Randomisation will be at the level of the individual using the method of minimisation stratified by: birth registered sex (male, female); tanner stage (stage 2/3, stage 4/5); diagnosis of a neurodevelopmental disorder or trait (yes, no); site (7-levels).

Randomisation will be undertaken by recruiting site staff, by authorised staff onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

### 7.1.3 Q-Interactive

Q-Interactive is the digital, cloud based platform used to administer cognitive assessments on a one-on-one basis using iPads in an app called Assess - The WISC-V will be administered using this method. One iPad is used by the researcher to view test instructions, score and record responses, and control visual stimuli; the second iPad is used by the participant to respond to stimuli. Test data is securely uploaded to Pearson's servers. The Q-interactive central is used for generating users and organising, reviewing, archiving, and exporting test results. Data will be transcribed from Q-interactive into the Medrio EDC by researchers based at recruiting sites.

## 7.2 Data security

### 7.2.1 Medrio and KCTU Randomisation System

The CI or delegate will request usernames and passwords from the KCTU for Medrio EDC/ePRO and Randomisation System. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the Trial Manager in the first instance.

Participant initials and date of birth will be entered on the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial.

### 7.2.2 Q-Interactive

Q-interactive adheres to strict data security standards to protect personally identifiable information (PII) and sensitive assessment data. Data is encrypted both in transit and at rest using industry-standard encryption protocols. User authentication requires strong credentials, and sessions are timed to log out automatically after periods of inactivity. Pearson complies with HIPAA, FERPA, and

other relevant data protection regulations to ensure that clinical information is handled in a secure and compliant manner. Data centres hosting Q-interactive services are certified under recognized security frameworks such as ISO 27001 and SOC 2. The system supports role-based access and user permissions to ensure that data may only be accessed and managed by authorised personnel. Participants' date of birth, study PIN and birth-registered sex will be entered into the system following confirmation and documentation of informed consent.

## 7.3 Data quality processes

### 7.3.1 Medrio EDC

At the database design stage, validations will be programmed into the systems to minimise data entry errors by querying the data entered in real time with sites.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst, where appropriate for the purpose of data cleaning and will request amendments to the Medrio EDC system data as required. No data will be amended independently of the study site responsible for entering the data.

Site staff will respond to data queries within the EDC as required. During site monitoring visits, the CRA will raise any queries with sites via the Source Data Verification (SDV) function.

The KCTU will provide the study team with a Data Management Plan (DMP) for Medrio EDC for filing in the TMF.

### 7.3.2 KCTU Randomisation System

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst for the purpose of data cleaning. No data can be amended in the system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

The KCTU will provide the study team with a DMP for the KCTU randomisation system once the system is made live.

### 7.3.3 Q-Interactive

Q-interactive has built-in checks to reduce scoring errors and standardise administration across users. The system automatically scores responses in real time and flags inconsistencies or incomplete data entries for review. Regular system updates and calibration procedures help preserve the accuracy of test materials and scoring. Digital administration minimises human error and ensures that data collected adheres to standardised protocols, enhancing the reliability and comparability of results.

## 7.4 Database lock

### 7.4.1 Medrio EDC

At the end of the trial, the site PIs will review all the data for each participant in the Medrio EDC system and provide electronic sign-off to verify that all the data are complete and correct.

The Trial Manager will confirm all checks are complete and all monitors queries have been resolved prior to database lock. At this point, with the agreement of the Senior Statistician, all data can be formally locked for analysis.

When the final data extract is requested, KCTU will remove all data entry user access prior to data extract and will retain only 'monitor' access for site PI's and other relevant individuals.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute to sites as appropriate. Once sites have received copies of their individual datasets and confirmation of receipt has been received, the Trial Manager will request that all user access is removed from the Medrio EDC system. A copy of the dataset will be stored in the TMF at the end of the study.

### 7.4.2 KCTU Randomisation System

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

### 7.4.3 Q-Interactive

Q-interactive features a database lock mechanism. Once an assessment session is finalized and uploaded to the Central platform, the data becomes read-only to prevent unauthorized alterations. This ensures an auditable, tamper-proof record of the session, supporting both clinical accountability and legal defensibility. In cases where data corrections are necessary, system administrators must follow defined procedures that log all changes and retain version histories for compliance and traceability.

At the end of the trial, assessment records will be exported from the Q-interactive platform as .csv files for storage. Once the dataset has been confirmed by the central PATHWAYS team, all relevant records from Q-interactive will be deleted.

## 7.5 MRI data management and storage (CONNECT)

MR images will be stored (pseudo-anonymised) on the Neuroimaging Analysis Network hosted at the Centre for Neuroimaging Sciences at KCL. This is a secure, password-protected dedicated server behind an institutional firewall with automated backups and archiving options. Access to the server will only made possible following study-specific and data governance training and with authorisation from the

CI. Data may also be stored on King's secured e-Research's Computational Research, Engineering and Technology Environment (CREATE).

# 8 Summary of known and potential risks of Triptorelin

Administration of Triptorelin for this study is not anticipated to induce any potential risk other than the known potential side effects listed below. Both CYP and adult profiles of side effects have been included as use of GnRHa for puberty suppression in transgender and gender diverse people is off-license, therefore consideration of all possible side effects will be required. Although there is no age specific information with regards to prevalence of side effects, Triptorelin is also used in the treatment of precocious puberty in children with an onset before 8 years in girls and 9 years in boys, and the SmPC was used to include known adverse reactions in this population (please refer to the most up to date SmPC). The same doses will be used in older children. The following adverse reactions have been noted with Triptorelin:

## 8.1 Side effects commonly reported

The following side effects are known to be commonly reported to Endocrinology Clinicians that have prescribed Triptorelin for those under the age of 18 years with a diagnosis of "Gender Incongruence" or "Gender Dysphoria" for the indication of puberty suppression. These have been collated from the expert endocrine panel as previously defined.

Common side effects reported clinically include unexpected PV bleeding (commonly referred to as spotting), hot flushes, increased perspiration, weight gain, injection site pain, mood changes, interrupted sleep, low mood, dizziness, fatigue, cyclic menstrual-like pelvic discomfort, breast tenderness, nausea, headache, reduced libido, and loss of spontaneous erections.

Common side effects reported of a subcutaneous injection are localised pain, swelling, sterile abscess, allergic reaction, muscular pain, induration and erythema.

## 8.2 Common side effects of Triptorelin

Common is defined as per BNF and BNFc standards with a frequency of between 1 in 100 to 1 into 10.

In under 18's, common side effects that have been reported are depression and altered mood.

In adults, common side effects are anxiety, asthenia, depression, diabetes mellitus, dizziness, dry mouth, embolism, gastrointestinal discomfort, gynaecomastia, haemorrhage, headache, hot flushes, hyperhidrosis, hypersensitivity, hypertension, joint disorders, menstrual cycle irregularities, altered mood, muscle complaints, nausea, oedema, ovarian and fallopian tube disorders, pain, painful sexual

intercourse, pelvic pain, sexual dysfunction, skin reactions, sleep disorders and weight changes.

## 8.3 Uncommon and rare side effects of Triptorelin

Uncommon is defined as per the BNF and BNFc standards with the frequency of between 1 in 1000 to 1 in 100. Rare is defined as a frequency between 1 in 10000 and 1 in 1000.

In under 18's, uncommon side effects are anaphylactic reaction, haemorrhage, nausea, vaginal discharge and vomiting.

Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving the IMP. Participants will be counselled to look out for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus. If suspected, the PI or delegated clinicians should make an urgent referral to ophthalmology.

In adults, uncommon side effects are alopecia, abnormal appetite, exacerbations of asthma, chills, confusion, constipation, diarrhoea, drowsiness, dyspnoea, flatulence, gout, muscle weakness, altered taste, testicular disorders, tinnitus, vertigo, vision disorders and vomiting.

In adults, rare side effects are abnormal eye sensation, chest pain, difficulty standing, fever, hypotension, influenza like illness, musculoskeletal stiffness, nasopharyngitis, orthopnoea, osteoarthritis and QT prolongation.

## 8.4 Side effects with unknown frequency of Triptorelin

An unknown frequency is defined as per the BNF and BNFc as that the frequency is not defined by the product literature or that the side-effect has been reported from post-marketing surveillance data.

In under 18's, side effects with an unknown frequency are alopecia, angioedema, epiphysiolysis, gastrointestinal discomfort, headache, hot flush, malaise, myalgia, nervousness, pain, skin reactions, vision disorders and increased weight.

## 8.5 Side effects of other GnRHa preparations

Leuprorelin acetate has similar side effect profiles to Triptorelin and are detailed in Appendix D.

Those commenced on Leuprorelin acetate and all GnRHa preparations should be counselled on the signs and symptoms of idiopathic intracranial hypertension (such as severe or recurrent headache, vomiting, visual disturbances and tinnitus) and increased risk of depression during use.

They should also be counselled on the signs and symptoms of severe cutaneous adverse reactions (SCARs) as treatment should be immediately discontinued if these occurs.

SCARs is inclusive of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) which can be life-threatening or fatal. Signs and symptoms include prodromal illness with fever, malaise, cough, rhinorrhoea, sore throat and sore eyes, an extensive and widespread rash that is itchy and painful with mucosal involvement that is erosive and haemorrhagic.

Rarely, seizures have been reported with GnRHa preparations. Participants with risk factors for seizures (such as a history of epilepsy, and structural brain abnormalities) should be monitored closely.

### 8.6 Treatment Interactions

There are no known drug interactions with Triptorelin or Leuprorelin acetate.

## 9 Adverse Event Management and Reporting

All adverse events will be recorded in the participant's medical notes, the study source data worksheets and the eCRF. All Adverse Events and Serious Adverse events will be recorded from the signing of the informed consent form until 12 weeks following the final dose. This reporting period reflects the prolonged pharmacological activity of the 6-month Triptorelin formulation. Events suspected to be related to the IMP occurring beyond this window should also be reported.

SAE's will be additionally reported, within 24 hours of site becoming aware of the event, to the KHP-CTO pharmacovigilance team.

All SAEs, SARs and SUSARs (except those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) as per the instructions on the SAE report form. SUSARs will be reported prospectively to the chair of the Data Monitoring Committee (DMC); all other safety events will be listed in DMC reports.

The sponsor will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- Adverse Event (AE): Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

- Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the SmPC for that product.
- Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:
    - results in death
    - is life-threatening
    - required hospitalisation or prolongation of existing hospitalisation
    - results in persistent or significant disability or incapacity
    - consists of a congenital anomaly or birth defect
- Important Medical Events (IME) & Pregnancy: Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

## 9.1 Reference Safety Information

The reference safety information (RSI) for PATHWAYS Trial is comprised of the SmPCs for Decapeptyl SR (long-acting formulation of Triptorelin) 22.5mg, Decapeptyl® SR (long-acting formulation of Triptorelin) 11.25mg, Prostap 3 DCS (Leuprorelin Acetate) 11.25mg, and Gonapeptyl (Triptorelin) 3.75mg. Specifically, the tables of ‘general tolerance in children’ are to be referred to for assessment of expectedness.

## 9.2 Evaluating AEs and SAEs

### Assessment of intensity

The PI or SI will assess intensity for each AE and SAE reported during the study. The assessment will be based on the PI/SI’s clinical judgement. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- **Mild**; An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- **Moderate**; An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe**; An event, which is incapacitating and prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

**Assessment of causality**

The Investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

- **Not Related**: In the Investigator's opinion, there is not a causal relationship between the study product and the AE.
- **Unlikely**: The temporal association between the AE and study product is such that the study product is not likely to have any reasonable association with the AE.
- **Possible**: The AE could have been caused by the study participant's clinical state or the study product.
- **Likely**: The AE follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study participant's clinical state.
- **Definitely**: The AE follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event prior to transmission of the SAE form to the Sponsor. The Investigator may change his/her opinion of causality considering follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Assessment of expectedness**

A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.

- **Expected**: An adverse reaction, the nature or severity of which is consistent with the applicable Reference Safety Information in the Summary of Product Characteristics for an approved medicinal product

- **Unexpected**: An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document

**Follow-up of AEs and SAEs**

After the initial AE/SAE report, the Investigator is required to proactively follow each participant and provide further information to the Sponsor on the participant's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the adverse event log will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the Investigator. The updated SAE form should be resent to the Sponsor.

**Post-study AEs and SAEs**

A post-study AE/SAE is defined as any event that occurs outside the AE/SAE detection period. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor.

## 9.3 Adverse event processing responsibilities

The sponsor has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) to the King's Health Partners Clinical Trials Office (KHP-CTO).

KHP-CTO will report SUSARs to the Research Ethics Committee (REC) and Medicines and Healthcare products Regulatory Agency (MHRA). Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported no later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The CI and KHP-CTO (on behalf of the co-sponsors) will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

The Trial Statistician will report relevant adverse events to the Data Monitoring Committee. Data on non-serious, severe ARs will be captured where causality is assessed as possible, likely, or definitely, and will be included in DMC reports.

# 10 Toxicity Management

Monitoring and Management of Adverse Events:

Regular Follow-Up: Participants will attend regular follow-up appointments to assess the efficacy and safety of the treatment. These appointments will include monitoring hormone levels, physical development assessments, routine blood tests, DEXA scans, and physical assessments (height, weight, BMI, blood pressure, and puberty staging).

Psychosocial Screening: Psychosocial screening to identify any unmet needs and escalate these to appropriate services.

Adverse Event Reporting: All adverse events will be recorded in the participants' medical notes, study source data worksheets, and the eCRF. Serious adverse events (SAEs) will be reported within 24 hours to the King's Health Partners Clinical Trials Office (KHP-CTO).

Management of Common Side Effects: Common side effects such as depression, altered mood, anxiety, and hot flushes will be monitored and managed according to clinical guidelines.

Management of Rare Side Effects: Rare side effects such as anaphylactic reactions, haemorrhage, and idiopathic intracranial hypertension will be monitored closely, and treatment will be discontinued if severe cutaneous adverse reactions (SCARs) occur.

Follow-Up of Adverse Events: All adverse events will be followed until resolution, stabilisation, or until the participant is lost to follow-up. Supplemental investigations may be conducted to elucidate the nature and causality of the adverse events.

# 11 Premature Termination of Trial

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the DMEC, PMC, regulatory authority, or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

# 12 Ethics Approval

This protocol and related documents will be submitted for review to Health Research Authority (HRA), REC and MHRA.

PATHWAYS TRIAL, HORIZON INTENSIVE and CONNECT will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and all of the applicable regulatory requirements (specify current legislation).

## 12.1 Protocol amendments and version control of study documents

The Trial Manager will be responsible for preparing and submitting protocol amendments to the ethics committee.

The Trial Manager will be responsible for updating the ISRCTN register following relevant protocol amendments.

Subsequent protocol amendments will be submitted to the REC and Regulatory Authorities for approval, and will comply with regulations, particularly specifying, Pharmacovigilance reporting and providing the REC & MHRA with progress reports, and a copy of the Final Study Report.

# 13 Statistical Methods

## 13.1 Trial

### 13.1.1 Primary Outcome

1. The primary outcome for the PATHWAYS TRIAL is the quality of life of children referred to national gender services for young people in the UK, measured using the CYP self-report version of the KIDSCREEN-10 questionnaire.

### 13.1.2 Secondary Outcomes

#### *13.1.2.1 Scales of Gender-Related Distress, Mental Health Symptoms and Physical Health measures :*

a. Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS)
b. Revised Children's Anxiety and Depression Scale (RCADS)
c. Body Image Scale – Gender Spectrum (BIS-GS)
d. Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y)
e. SCOFF questionnaire
f. Sexual attraction questionnaire
g. ALSPAC measure
h. Gender identity question
i. Adolescent Primary Care Traumatic Stress Screen (APCTSS)
j. KIDSCREEN-52
k. Height (cm) and weight (kg)

l. Physical health diagnoses

### 13.1.3 Scales of Suicidal Ideation, Hospitalizations, Mood Symptoms, Behavioural and Functional Difficulties:

a. Ask Suicide-screening Questions (ASQ)
b. Child Behaviour Checklist (CBCL)
c. Youth Self-Report (YSR)
d. Difficulties in Emotion Regulation Scale – 18 (DERS-18)
e. Hospitalisations of participants

### 13.1.4 Experiences of Therapeutic Options:

a. Rates of referral to, uptake of, and completion of psychological therapy, occupational therapy, speech and language therapy, clinical nursing, youth work support, school/college support, and non-endocrine pharmacological treatments.

### 13.1.5 Cognitive Assessments

a) Wechsler Intelligence Scale for Children (WISC-V)
b) Delis-Kaplan Executive Function System (D-KEFS)
c) Child and Adolescent Memory Profile (CHAMP)
d) Memory Validity Profile (MVP)
e) Behaviour Rating Inventory of Executive Function (BRIEF)

### 13.1.6 Continuous Physical Measures

a) Height (cm)
b) Weight (kg)
c) BMI
d) Bone mineral density (DEXA) z score
e) Blood pressure; systolic, diastolic, mean
f) Safety bloods

### 13.1.7 Binary Physical Outcomes

a) Adverse events
b) Puberty staging (Tanner staging, both clinical and self-reported)

## 13.2 HORIZON INTENSIVE

### 13.2.1 Primary Outcome

1. The primary outcome for PATHWAYS HORIZON INTENSIVE is the quality of life of children referred to national gender services for young people in the UK, measured using the CYP self-report version of the KIDSCREEN-10 questionnaire.

### 13.2.2 Scales of Gender-Related Distress, Mental Health Symptoms and Physical Health measures:

a. Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS)
b. Revised Children's Anxiety and Depression Scale (RCADS)
c. Body Image Scale – Gender Spectrum (BIS-GS)
d. Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES-Y)
e. SCOFF questionnaire
f. Sexual attraction questionnaire
g. ALSPAC measure
h. Gender identity question
i. Adolescent Primary Care Traumatic Stress Screen (APCTSS)
j. KIDSCREEN-52
k. Height (cm) and weight (kg)
l. Physical health diagnoses

### 13.2.3 Rates of Suicidal Ideation, Non-Suicidal Self-Injury, Hospitalizations, Mood Symptoms, Behavioural and Functional Difficulties:

a. Ask Suicide-screening Questions (ASQ)
b. Child Behaviour Checklist (CBCL)
c. Youth Self-Report (YSR)
d. Difficulties in Emotion Regulation Scale – 18 (DERS-18 for CYP; DERS-29 for parents/caregivers)
e. Hospitalisations of participants

### 13.2.4 Experiences of Therapeutic Options:

a. Rates of referral to, uptake of, and completion of psychological therapy, occupational therapy, speech and language therapy, clinical nursing, youth work support, school/college support, and non-endocrine pharmacological treatments.

### 13.2.5 Cognitive Assessments:

a. Wechsler Intelligence Scale for Children (WISC-V)
b. Delis-Kaplan Executive Function System (D-KEFS)
c. Child and Adolescent Memory Profile (CHAMP)
d. Memory Validity Profile (MVP)
e. Behaviour Rating Inventory of Executive Function (BRIEF)

### 13.2.6 Continuous Physical Measures:

a. Height (cm)
b. Weight (kg)
c. BMI
d. Bone mineral density (DEXA) z score
e. Blood pressure; systolic, diastolic, mean
f. Safety bloods

### 13.2.7 Binary Physical Outcomes:

a. Adverse events
b. Puberty staging (self-reported)

## 13.3 CONNECT

a. Brain Structure: Longitudinal trajectories of brain tissue volume (especially in the basal ganglia, pituitary gland and hypothalamus) using standard weighted T1 and T2 images.

b. Brain Structure: Longitudinal trajectories of microstructure in cortical white matter using diffusion MRI and T2* images.

c. Brain Metabolites: Longitudinal changes in brain metabolites in the globus pallidus and putamen (basal ganglia) using magnetic resonance spectroscopy.

d. Brain function: Functional connectivity between the basal ganglia (and other sub-cortical structures) with cortex using functional MRI.

These outcomes are exploratory and there is no defined primary outcome.

Longitudinal brain trajectories will be investigated for associations to cognitive measures (general intelligence, executive functioning and memory).

## 13.4 Sample size justification

### 13.4.1 Trial

The anticipated sample size 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 the equivalent of 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, the probability of detecting the same SES will be lower. If only 150 participants are recruited, the trial would still have the equivalent of 80% power to detect the SES of 0.525.

As the eligibility criteria for the trial cannot be changed or widened as would be common in a poorly recruiting trial, nor more sites added, other options would have to be considered to reach the target sample size of 226. This could include extending the recruitment period and therefore timeline for the trial. Interim analyses can also be carried out at pre-specified points where decisions on the continuation of the trial can be taken. All amendments to the trial will be approved by both the DMC and the PSC committees before being enacted.

### 13.4.2 HORIZON INTENSIVE

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(substituting chronological age as a proxy for Tanner stage). This will be done by recruiting participants to HORIZON INTENSIVE at intervals, after assessing the general stratification factors of participants randomised into the trial.

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 the equivalent of 90% power (300 vs 112). We will have the equivalent of 90% power to detect a 0.32 SES for intensive participants to be tested against the whole trial population (300 vs 226).

### 13.4.3 CONNECT

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 eta2=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). With a sample size (minimum) per group of 49 across all 3 time points, the study is well powered ($a<0.001$, $b>0.9$) to detect interactions between treatment group and volumetry over the 3 timepoints while also allowing for multiple testing / comparison correction (calculated using G*Power).

We will also use a normative modelling approach to understand individual differences in brain development in CYP[47]. In the absence of prior data in the same age range and characteristics, we estimate effect size by comparing n = 89 children with born prematurely to a term-born volumetric growth curve of healthy children derived from n = 275 using Gaussian process regression. This found a large effect size versus 0 (preterm mean Z = 1.78 and SD of Z = 1.94, cliff's delta = 0.62). Assuming a medium effect size of GnRHa treatment on brain tissue volumes (Cohen d = 0.5) and with alpha = 0.05 and beta (power) = 0.9, we would need a sample size of n=36. Assuming a more realistic small effect size (Cohen d = 0.3) and with alpha = 0.05 and beta (power) = 0.9, we would need a sample size of n=97.

## 13.5 Statistical methods for primary and secondary outcomes

### 13.5.1 Statistical methods for primary outcome

#### *13.5.1.1 Trial*

The primary estimand is a treatment policy estimand. This means that intercurrent events are not taken into account when the analysis is performed. This is similar to how an intention to treat analysis would be carried out. The specification of the estimand is below.

- **Population** – CYP with gender dysphoria who are in the CYPGS and are determined to be clinically eligible for GnRHa treatment and meet the eligibility criteria for the trial.
- **Endpoint** – The endpoint is 24-months post randomisation into the trial.
- **Treatment condition** – Treatment is GnRHa, either immediately or delayed for a year. The delayed treatment is the control treatment, and the treatment arm is the immediate arm.
- **Intercurrent event** – Intercurrent events are as below:
    - Failure to adhere to randomised treatment protocol – Non-compliance with the prescribed treatment regimen, including missed doses or incorrect administration
    - Premature discontinuation of the randomised treatment – Participants stopping the treatment before the study endpoint for any reason.
    - Death of participant during the trial period
    - Long-term physical or mental health hospital admission – Hospital admissions for physical health reasons that extend beyond a short-term stay and could impact the study outcomes
    - Serious adverse events that significantly impact the participant's health and require medical intervention (such as a severe allergic reaction)
    - Substance abuse: Development of substance abuse issues during the trial period
    - Pregnancy
    - Major changes in lifestyle or environment that could impact the participant's health or adherence to the trial protocol, such as relocation
- **Population level summary** – The population level summary will be the difference between the two arms at 24-months, as measured by the mean of the posterior, with the 95% credible interval.

The analysis of the primary outcome will be carried out using the Bayesian framework. Using the Bayesian framework means that the analysis will have to specify priors and allows for the analysis to give credible intervals, as opposed to confidence intervals, that are much easier to interpret.

The primary analysis model will be a Bayesian linear mixed model. The baseline score for the primary outcome will be included as a fixed effect, alongside the stratifying factors of site, birth registered sex, tanner stage and diagnosis of a neurodevelopmental disorder or trait. Random effects for participant will be included to account for clustering of longitudinal data within participants.

As this will be carried out using the Bayesian framework, priors used for all parameters estimated will be uninformative, flat priors. Derivation of the single primary outcome is detailed fully in the PATHWAYS TRIAL Statistical Analysis Plan.

#### *13.5.1.2 HORIZON INTENSIVE*

The primary outcome for HORIZON INTENSIVE is the KIDSCREEN-10. Analysis will be carried out in the same fashion as the Horizon trial, using a Bayesian linear mixed model within a Bayesian framework. Stratifying factors will be used as fixed effects and participant will be used as a random effect to allow for the clustered nature of repeated measures data. Priors will be uninformative. As the HORIZON INTENSIVE cohort is loosely matched to trial participants, this matching will be taken into consideration.

#### *13.5.1.3 CONNECT*

To assess whether the effect of GnRHa acts over and above the effect of age on the brain during puberty, mapping and comparison of brain structure, functional and metabolite trajectories in each study arm will be performed to establish effects of the treatment group. The model will include age, Tanner stage and birth-registered sex.

The approach will be to either restrict a-priori defined variables for confirmatory hypothesis testing or full reporting of all comparisons for exploratory research. GnRHa/no-GnRHa comparisons of brain imaging data will be made to establish mean group differences in individuals matched as far as possible for age and sex-registered at birth. This will be performed using linear mixed effect models, with subject as the random effect, and age, Tanner stage at time one and GnRHa treatment status (yes/no) as fixed effects. In secondary exploratory analysis, incorporated in the design matrices will be continuous variables such as change in cognitive function measures to examine outcome prediction pathways respectively.

### 13.5.2 Statistical methods for secondary outcome

#### *13.5.2.1 Continuous outcomes*

13.5.2.1.1 Trial

Continuous secondary outcomes will be analysed using the same estimand using the treatment policy intercurrent event handling method. The same method of analysis will also be used, maintaining the same fixed and random effect structure as the primary outcome analysis. Uninformative priors will also be used for parameters that are to be estimated.

13.5.2.1.2 HORIZON INTENSIVE

Continuous secondary outcomes will follow the same analysis plan as the primary analysis.

#### *13.5.2.2 Binary outcomes*

13.5.2.2.1 TRIAL

Binary secondary outcomes will be analysed using the same approach as the primary analysis. The estimand will be the same as the primary analysis, utilising the treatment policy intercurrent event handling method. The analysis carried out shall use a logistic mixed model, still retaining the fixed and random effect structure of the

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

primary analysis. Uninformative priors will be used for parameters that are to be estimated.

13.5.2.2.2 HORIZON INTENSIVE

Binary secondary outcomes will use the same fixed and random effects, and uninformative priors. Instead of a linear mixed model, a logistic mixed model will be used. Other outcomes not falling into these categories will reflect the analysis methods used in the trial.

### 13.5.3 Statistical methods for exploratory analyses

#### *13.5.3.1 CONNECT*

To explore individual differences, a normative modelling framework has been developed by CONNECT researchers for use in multimodal neonatal brain imaging data, that is both sensitive to brain growth and the diffuse brain changes seen following prematurity and in individuals with autism across childhood and adulthood. This approach provides an individual index of variation from the typical distribution from as early as birth, corrected for age or sex, per modality and region, capturing inter-person heterogeneity. This measure of variation has also proven a useful intermediate phenotype to interrogate pathways out to cognitive function in early life. An important advantage of our approach is that we can develop growth curves across different MRI modalities. We will use 'normative modelling' (Gaussian Process Regression or similar Bayesian approach) to assess brain maturation of patients in each study arm with reference to adolescent brain structural, functional and metabolite reference values built from existing studies. An individual Z-score then captures deviations from age-expected reference and can be used to examine either correlations with outcome measures or individual differences in brain changes with respect to GnRHa.

## 13.6 Adherence

To be defined in the Statistical Analysis Plan.

## 13.7 Interim analyses (statistical)

Currently, no interim analysis is planned either for futility or for efficacy in either TRIAL or HORIZON INTENSIVE. By using the Bayesian framework for analyses, there is no penalty in the form of type 1 error which is common for frequentist approaches, and as such does not need to be factored in to sample size calculations.

Interim analyses therefore may happen, but only at the recommendation of the DMC and the PSC (or the funder, via the PSC). Only data which the DMC and PSC deem relevant will be analysed at these timepoints. These are the only two committees that may call for an interim analysis of the data. If these committees do not call for interim analyses during TRIAL or HORIZON INTENSIVE, then no interim analyses will be carried out.

If an interim analysis is deemed appropriate, then the results of any such analysis will be shared with the DMC only in the first instance. It is then within the remit of the DMC to determine if it is important for the PSC or PMG should see the results. For example, if a decision is to be made based on the interim analyses, the DMC will make their recommendation to the PSC and depending on the strength of evidence from the data, may determine that the PSC does not need to see the data as there is no ambiguity.

If a decision is to be made, the PSC will advise the sponsor in making the final decision on stopping, continuation, or any potential extension to the funding period.

## 13.8 Methods for additional analyses (e.g. subgroup analyses)

Subgroup analyses will include looking at the stratifying factors of Tanner stage (2/3 vs 4/5), birth registered sex (male/female), and whether there is a neurodevelopmental trait or disorder diagnosis (yes/no). Also assessed will be the length of GnRHa treatment received over the duration of the trial.

The statistical analysis plans for the respective studies will further define subgroups to be analysed, and the analysis to be carried out on these subgroups.

## 13.9 Methods to handle missing data

Where there are two or more post randomisation outcome timepoints, missing assessments will be dealt with by fitting mixed models to all the available data using maximum likelihood methods. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or Missing At Random, MAR). This approach applies to both TRIAL and HORIZON INTENSIVE.

## 13.10 Populations under investigation

### 13.10.1 TRIAL

For TRIAL and CONNECT, all participants randomised will be analysed in the arms which they were randomised to regardless of the intervention they received, under the treatment policy estimand.

### 13.10.2 HORIZON INTENSIVE

HORIZON INTENSIVE participants will all be analysed in the same arm, as there is no intervention they can receive.

## 13.11 Methods to handle compliance

Compliance will be defined in the SAP. Non-compliance will be dealt with using sensitivity analyses. These analyses are detailed in section 13.12.

### 13.12 Sensitivity analysis

A Complier Average Causal Effect (CACE) analysis on the primary outcome will be performed if adherence is found to be low (less than 80% in the study overall). This will only be for Trial analysis.

Additional analyses will be carried out using alternative priors, to assess the robustness of the estimates obtained in the primary analysis. These priors will be used in place of the uninformative priors being used in the primary analysis.

### 13.13 Plans to give access to the full protocol and participant-level data

It is anticipated the full protocol and all results will be available as open access according to the rules of the funding bodies.

## 14 Oversight and monitoring

### 14.1 Programme Management Group (PMG)

The PMG will be chaired by the PATHWAYS CI, Professor Emily Simonoff, with membership comprising co-investigators and core members of the central research team.

### 14.2 Programme Steering Committee (PSC)

The PSC will be composed of 7 independent members and additional non-independent members; the independence level will be above 75%. Attendance of non-voting members at PSC meetings will be at the discretion of the chair. The PSC is an executive committee, reporting to the funder, the National Research Collaboration Programme (NRCP), and the trial sponsors.

The PSC is formally appointed by the National Institute for Health and Care Research (NIHR) and members will receive individual letters from the NIHR confirming their role. Independent members will be independent of the Sponsor organisations and of any recruiting study sites.

The PSC will agree the frequency of meetings prior to the start of the trial; however, it is likely the PSC will meet at least bi-annually.

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Programme Steering Committee regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed, and no further participant data will be collected. The Competent Authority and REC will be informed within 15 days of the early termination of the trial.

### 14.3 Data Monitoring Committee (DMC)

The DMC will be composed of five independent members: a statistician and two clinicians. The DMC is an advisory committee, reporting to the PSC. The DMC membership is formally appointed by NIHR and members will receive individual letters from the NIHR confirming their role. Members will be independent of the Sponsor organisations and of any recruiting study sites. The DMC will work to the DAMOCLES guidance[48].

The DMC will agree the frequency of meetings prior to the start of the trial; however, it is likely the DMC will meet at least bi-annually.

The DMC will assess adverse event data and can recommend a pause of enrolment and/or IMP dosing whilst it adjudicates relatedness and severity of safety events.

### 14.4 Monitoring

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g., participants' case sheets, blood test reports etc.)

## 15 Miscellaneous

### 15.1 Plans for independent audit

There are no current plans to commission an independent audit study conduct.

### 15.2 Dissemination plans

Findings from the study will be published in peer-reviewed scientific journals, with open access in all cases. For all scientific papers, we will develop an accessible, easy-read version of the findings, suitable for the lay audience, including the CYP attending the CYPGS. The latter will be developed in collaboration with our PATHWAYS Engagement Advisory Groups.

The primary and secondary outcomes will be published in a peer reviewed open-source medical journal within 12 months of the end of trial. Recruiting sites will be informed of the results and will be asked to disseminate the findings to participants. Patient groups will be informed of the results for dissemination among their members.

Results will also be presented at a range of scientific and community-facing conferences. The funders will be informed about oral presentations in advance.

### 15.3 End of trial

The end of the trial will be defined as database lock.

## 15.4 Confidentiality

When consent forms are signed, a copy will be provided to the participant, a copy will be filed in the medical records and the original will be retained in the Investigator Site File. Participant's year of birth and age will be entered into the study database from countries where this is permitted, but no more identifying information will be collected outside the recruiting study site. An Investigator Site File will be maintained by the PI at recruiting sites. Participants will be fully identifiable within these files.

When the study is complete, a data sharing dataset will be created from the raw data by the study analyst, which will not include any other identifiable data and study PIN will be altered so that individuals are not recognisable from the dataset.

The study will comply with the General Data Protection Regulations (GDPR).

## 15.5 Funding

PATHWAYS is funded by the National Research Collaboration Programme (NRCP), an NHS England and NIHR partnership. The views expressed are those of the author(s) and not necessarily those of NHS England, NIHR or the Department of Health and Social Care.

Long-Term Safety Monitoring via Registry Linkage:

To address potential long-latency outcomes (e.g., bone health, fertility, cognitive development), participants will be invited to consent to long-term follow-up through linkage with national health registries and routinely collected NHS digital datasets. This approach minimises participant burden while enabling systematic capture of clinically relevant endpoints such as fracture incidence, fertility-related interventions, and major health events. Active study follow-up will continue for up to the duration of the study. Post-randomisation; thereafter, data will be obtained passively via registry linkage, subject to participant consent and applicable legal regulations. Participants will be informed of this plan in the Participant Information Sheet and Informed Consent Form, including the option to withdraw from registry follow-up at any time without affecting their clinical care.

## 15.6 Availability of data and materials

Data will not be available to other parties during the period of data collection and analyses and publication addressing the objectives outlined above. Following completion of the study and publication of these results, consideration will be given to providing anonymised data to other researchers following a written application.

The protocol will be published in an open-access journal, providing an accessible version of the information in this document that will aid other researchers in the field who may wish to consider using data generated from PATHWAYS TRIAL/CONNECT/HORIZON INTENSIVE.

## 15.7 Insurance and indemnity

King's College London provides no fault liability insurance in the event of harm arising from the study design. UK NHS recruiting sites provide indemnity in the event of clinical negligence.

## 15.8 Archiving

At the end of the trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving Standard Operating Procedure (SOP).

Recruiting sites will be responsible for archiving the source data, Investigator Site Files and Pharmacy Site Files. The PI at each site holds responsibility for ensuring ISFs, source data, and pharmacy files are archived properly until written permission for destruction of files is provided by the sponsor at the end of the retention period of 25 years. Similarly, the TMF will be archived for the retention period of 25 years until written permission for destruction is provided by the sponsor.

# 16 References

1. World Health Organization. International classification of diseases (11th revision). 2022.
2. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). DSM-5 Criteria for Gender Dysphoria: American Psychiatric Publishing; 2013.
3. Zucker KJ. Epidemiology of gender dysphoria and transgender identity. Sexual health. 2017;14(5):404-11.
4. Cass H. The Cass Review: Independent review of gender identity services for children and young people: Final report.; 2024.
5. Taylor J, Hall R, Langton T, Fraser L, Hewitt CE. Care pathways of children and adolescents referred to specialist gender services: a systematic review. Archives of Disease in Childhood. 2024.
6. Appleby L. Review of suicides and gender dysphoria at the Tavistock and Portman NHS Foundation Trust: independent report Published. 2024.

7. Taylor J, Mitchell A, Hall R, Heathcote C, Langton T, Fraser L, et al. Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review. Archives of Disease in Childhood. 2024.
8. Taylor J, Mitchell A, Hall R, Langton T, Fraser L, Hewitt CE. Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: a systematic review. Archives of Disease in Childhood. 2024.
9. Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. N Engl J Med. 2020;382(7):674-8.
10. Fulchand S. Children with cancer are missing out on precision medicine, study finds. BMJ. 2019;366:l5696.
11. Modi N, Clark H, Wolfe I, Costello A, Budge H, Goodier R, et al. A healthy nation: strengthening child health research in the UK. Lancet. 2013;381(9860):73-87.
12. Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. Journal of Pediatric Endocrinology and Metabolism. 2019;32(10):1077-81.
13. Stoffers IE, de Vries MC, Hannema SE. Physical changes, laboratory parameters, and bone mineral density during testosterone treatment in adolescents with gender dysphoria. The journal of sexual medicine. 2019;16(9):1459-68.
14. Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. PloS one. 2021;16(2):e0243894.
15. Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. The journal of sexual medicine. 2015;12(11):2206-14.
16. Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental health outcomes in transgender and nonbinary youths receiving gender-affirming care. JAMA network open. 2022;5(2):e220978-e.

17. White SW, Lerner MD, McLeod BD, Wood JJ, Ginsburg GS, Kerns C, et al. Anxiety in youth with and without autism spectrum disorder: Examination of factorial equivalence. Behavior therapy. 2015;46(1):40-53.
18. Zhou X, Teng T, Zhang Y, Del Giovane C, Furukawa TA, Weisz JR, et al. Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. The Lancet Psychiatry. 2020;7(7):581-601.
19. Mul D, Versluis-den Bieman H, Slijper F, Oostdijk W, Waelkens J, Drop S. Psychological assessments before and after treatment of early puberty in adopted children. Acta Paediatrica. 2001;90(9):965-71.
20. Schneider MA, Spritzer PM, Soll BMB, Fontanari AM, Carneiro M, Tovar-Moll F, et al. Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression. Frontiers in Human Neuroscience. 2017;11:528.
21. Strang JF, Chen D, Nelson E, Leibowitz SF, Nahata L, Anthony LG, et al. Transgender youth executive functioning: relationships with anxiety symptoms, autism spectrum disorder, and gender-affirming medical treatment status. Child Psychiatry & Human Development. 2022;53(6):1252-65.
22. Swanson JM, Schuck S, Porter MM, Carlson C, Hartman CA, Sergeant JA, et al. Categorical and dimensional definitions and evaluations of symptoms of ADHD: history of the SNAP and the SWAN rating scales. The International journal of educational and psychological assessment. 2012;10(1):51.
23. Office GE. National LGBT survey: Summary Report. In: Office GE, editor. 2018.
24. Rutter M. The Social Communication Questionnaire. Western Psychological Services. 2003.
25. Ravens-Sieberer U, Herdman M, Devine J, Otto C, Bullinger M, Rose M, et al. The European KIDSCREEN approach to measure quality of life and well-being in children: development, current application, and future advances. Quality of life research. 2014;23:791-803.
26. Forbes G, Lord C, Elias R, Pickles A. Predicting uncertain multi-dimensional adulthood outcomes from childhood and adolescent data in people referred to autism services. Frontiers in Psychology. 2021;12:594462.
27. Ng LC, Oblath R, Brigham R, Tai MH, Coles M. Development and pilot testing of a five item traumatic stress screener for use with adolescents in pediatric primary care. Child and Adolescent Psychiatry and Mental Health. 2022;16(1):71.
28. Ebesutani C, Korathu-Larson P, Nakamura BJ, Higa-McMillan C, Chorpita B. The revised child anxiety and depression scale 25–parent version: scale development and validation in a school-based and clinical sample. Assessment. 2017;24(6):712-28.
29. Achenbach TM, Rescorla L. Child behavior checklist for ages 6-18: University of Vermont Burlington, VT; 2001.
30. McGuire JK, Berg D, Catalpa JM, Morrow QJ, Fish JN, Nic Rider G, et al. Utrecht Gender Dysphoria Scale-Gender Spectrum (UGDS-GS): construct validity among transgender, nonbinary, and LGBQ samples. International Journal of Transgender Health. 2020;21(2):194-208.
31. McGuire J, Spencer, K., Rider, G. N., & Berg, D. Body image scale – Gender spectrum. 2016.

32. Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. Archives of sexual behavior. 1975;4:639-56.
33. Horowitz LM, Bridge JA, Teach SJ, Ballard E, Klima J, Rosenstein DL, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. Archives of pediatrics & adolescent medicine. 2012;166(12):1170-6.
34. Morgan JF, Reid F, Lacey JH. The SCOFF questionnaire: assessment of a new screening tool for eating disorders. Bmj. 1999;319(7223):1467-8.
35. Victor SE, Klonsky ED. Validation of a brief version of the difficulties in emotion regulation scale (DERS-18) in five samples. Journal of psychopathology and Behavioral Assessment. 2016;38:582-9.
36. Xu Y, Norton S, Rahman Q. Adolescent sexual behavior patterns in a British birth cohort: A latent class analysis. Archives of sexual behavior. 2021;50:161-80.
37. Hansen WB, Paskett ED, Carter LJ. The Adolescent Sexual Activity Index (ASAI): A standardized strategy for measuring interpersonal heterosexual behaviors among youth. Health Education Research. 1999;14(4):485-90.
38. Hidalgo MA, Chen D, Garofalo R, Forbes C. Perceived parental attitudes of gender expansiveness: Development and preliminary factor structure of a self-report youth questionnaire. Transgender Health. 2017;2(1):180-7.
39. Reguitti V, Poquiz JL, Jackson K, Coyne CA, Hidalgo MA, Forbes C, et al. Preliminary factor structure of the parental attitudes of gender expansiveness scale for parents (PAGES-P). Clinical practice in pediatric psychology. 2022;10(1):1-8.
40. Wechsler D. Wechsler, D. (2014). Wechlser Intelligence Scale for Children. 5th edn: Psychological Corporation. 2014.
41. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan executive function system. Assessment. 2001.
42. Sherman E, Brooks B. Child and adolescent memory profile (ChAMP). Psychological Assessment Resources, Inc. 2015.
43. Brooks BL, Sherman EM. Using the Memory Validity Profile (MVP) to detect invalid performance in youth with mild traumatic brain injury. Applied Neuropsychology: Child. 2019;8(4):319-25.
44. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior Rating Inventory of Executive Function® Second Edition. PsycTESTS Dataset. 2015.
45. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Test review behavior rating inventory of executive function. Child neuropsychology. 2000;6(3):235-8.
46. Carel J-C, Léger J. Precocious puberty. New England Journal of Medicine. 2008;358(22):2366-77.
47. .

# APPENDIX A – Individual schedule of events

***Table 4. Schedule of events for immediate GnRHa treatment arm***

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Registration form & consent | X | | | | | | | | | | |
| Eligibility | | X | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | |
| BASELINE CHARACTERISTICS # | | | | | | | | | | | |
| ADHD (SNAP-IV) | | X | | | | | | | | | |
| Autism (SCQ) | | X | | | | | | | | | |
| About Yourself Questionnaire | | X | | | | | | | | | |
| Status form | | | X | X | X | X | X | X | X | X | |
| QUESTIONNAIRES | | | | | | | | | | | |
| Quality of Life (KIDSCREEN-10) | | X | | X | | X | | X | | X | X### |
| KIDSCREEN-52 – all domains | | X | | X | | X | | X | | X | X### |
| Personal priorities | | X | | | | X | | | | X | X### |
| Gender Identity Questionnaire^^^ | | X | | | | X | | | | X | X### |
| Social Transition Questionnaire | | X | | | | X | | | | X | X### |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Anxiety and depression symptoms (RCADS-25) | | X | X | X | | X | X | X | | X | X### |
| Suicide/ Self Harm (ASQ) | | X | X | X | | X | X | X | | X | X### |
| Gender dysphoria (UGDS-GS) | | X | | | | X | | | | X | X### |
| Body image/ dysphoria (BIS-GS) | | X | | | | X | | | | X | X### |
| Emotional Dysregulation (DERS-18) | | X | | | | X | | | | X | X### |
| Sexual Attraction Questionnaire | | X | | | | X | | | | X | X### |
| Romantic Relations (ALSPAC measure) | | X | | | | X | | | | X | X### |
| Parental support (PAGES) | | X | | | | X | | | | X | X### |
| Trauma (APCTSS) | | X | | | | X | | | | X | X### |
| Emotional & Behavioural Problems (CBCL, YSR) | | X | | | | X | | | | X | X### |
| Eating Problems (SCOFF) | | X | | | | X | | | | X | X### |
| SCANS | | | | | | | | | | | |
| DEXA | X | X | | | | X | | | | X | X### |
| Bone Age Scan (X-Ray) | X | X | | | | X^ | | | | X^ | |
| CLINICAL MEASURES | | | | | | | | | | | |
| Tanner Staging** | X | X | | | | X | | | | X | |
| Self-reported puberty staging assessment | | X | | | | X | | | | X | |
| Physical examination | X | X | | X | | X | | X | | X | |
| ***Vital signs | X | X | | X | | X | | X | | X | |
| ECG | X | | | | | | | | | | |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Review of systems (history and examination) | | X | | X | | X | | X | | X | |
| (Optional) Body Composition - Tanita Scale | | X | | X | | X | | X | | X | |
| Telephone check-in | | | X | | X | | X | | X | | |
| Safety bloods | X | X | | X | | X | | X | | X | |
| ***Pregnancy test (pocbp)++ | X | X | | X | | X | | X | | X | |
| Urinalysis | X | X | | X | | X | | X | | X | |
| COGNITIVE MEASURES | | | | | | | | | | | |
| General Intelligence – WISC V | | X | | | | X | | | | X | |
| Inhibition, shifting, verbal fluency – D-KEFS | | X | | | | X | | | | X | |
| Memory: visual recognition, verbal recall - CHAMP | | X | | | | X | | | | X | |
| Memory validity profile - MVP | | X | | | | X | | | | X | |
| Executive functions at home - BRIEF | | X | | | | X | | | | X | |
| MAGNETIC RESONANCE IMAGING (PATHWAYS CONNECT) | | | | | | | | | | | |
| Structural/functional Imaging – s/fMRI | | X | | | | X | | | | X^^ | |
| ONGOING | | | | | | | | | | | |
| ***Adverse events log | | | | | | | | | | | X |
| ***Concomitant medications log | | | | | | | | | | | X |
| Withdrawal form | | | | | | | | | | | X |
| PHARMACY | | | | | | | | | | | |
| Study medication dispensing/administration | | X | | X | X+++ | X | X+++ | X | X+++ | X | |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Study medication dosing log | | | | | | | | | | | X |

**Legend**

# Not required if already captured as part of PATHWAYS HORIZON
* All ongoing forms to be reviewed and updated at each visit
** Tanner staging assessments optional at Months 12 & 24
***Safety review including vital signs, adverse event reporting, concomitant medication review, pregnancy test (POCBP only) at every injection visit for participants switching to 3-monthly or monthly IMP preparation.
### Ongoing questionnaires and DEXA scans completed annually during follow up period

++ People of child bearing potential only
+++ Dispensing at Months 9,15,21 if changing to 3 monthly preparation
^ Bone age scan at M12 & M24 optional
^^ Visit window for final scan of 6 weeks prior to/following final treatment injection
^^^Gender Identity Questionnaire completed only at baseline for Parents

***Table 5. Schedule of events for delayed GnRHa treatment arm***

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Registration form & consent | X | | | | | | | | | | |
| Eligibility | | X | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | |
| BASELINE CHARACTERISTICS # | | | | | | | | | | | |
| ADHD (SNAP-IV) | | X | | | | | | | | | |
| Autism (SCQ) | | X | | | | | | | | | |
| About Yourself Questionnaire | | X | | | | | | | | | |
| Status form | | | X | X | | X | X | X | | X | |
| QUESTIONNAIRES | | | | | | | | | | | |
| Quality of Life (KIDSCREEN-10) | | X | | X | | X | | X | | X | X[###] |
| KIDSCREEN-52 – all domains | | X | | X | | X | | X | | X | X[###] |
| Personal priorities | | X | | | | X | | | | X | X[###] |
| Gender Identity Questionnaire^^^ | | X | | | | X | | | | X | X[###] |
| Social Transition Questionnaire | | X | | | | X | | | | X | X[###] |
| Anxiety and depression symptoms (RCADS-25) | | X | X | X | | X | X | X | | X | X[###] |
| Suicide/ Self Harm (ASQ) | | X | X | X | | X | X | X | | X | X[###] |
| Gender dysphoria (UGDS-GS) | | X | | | | X | | | | X | X[###] |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Body image/ dysphoria (BIS-GS) | | X | | | | X | | | | X | X ### |
| Emotional Dysregulation (DERS-18) | | X | | | | X | | | | X | X ### |
| Sexual Attraction Questionnaire | | X | | | | X | | | | X | X ### |
| Romantic Relations (ALSPAC measure) | | X | | | | X | | | | X | X ### |
| Parental support (PAGES) | | X | | | | X | | | | X | X ### |
| Trauma (APCTSS) | | X | | | | X | | | | X | X ### |
| Emotional & Behavioural Problems (CBCL, YSR) | | X | | | | X | | | | X | X ### |
| Eating Problems (SCOFF) | | X | | | | X | | | | X | X ### |
| SCANS | | | | | | | | | | | |
| DEXA | X | X | | | | X | | | | X | X ### |
| Bone Age Scan (X-Ray) | X | X | | | | X^ | | | | X^ | |
| CLINICAL MEASURES | | | | | | | | | | | |
| Tanner Staging** | X | X | | | | X | | | | X | |
| Self-reported puberty staging assessment | | X | | | | X | | | | X | |
| Physical examination | X | X | | | | X | | X | | X | |
| ***Vital signs | X | X | | | | X | | X | | X | |
| ECG | X | | | | | | | | | | |
| Review of systems (history and examination) | | X | | | | X | | X | | X | |
| (Optional) Body Composition - Tanita Scale | | X | | | | X | | X | | X | |
| Telephone check-in | | | X | | X | | X | | X | | |
| Safety bloods | X | X | | | | X | | X | | X | |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Pregnancy test (pocbp)++ | X | X | | | | X | | X | | X | |
| Urinalysis | X | X | | | | X | | X | | X | |
| COGNITIVE MEASURES | | | | | | | | | | | |
| General Intelligence – WISC V | | X | | | | X | | | | X | |
| Inhibition, shifting, verbal fluency – D-KEFS | | X | | | | X | | | | X | |
| Memory: visual recognition, verbal recall - CHAMP | | X | | | | X | | | | X | |
| Memory validity profile - MVP | | X | | | | X | | | | X | |
| Executive functions at home - BRIEF | | X | | | | X | | | | X | |
| MAGNETIC RESONANCE IMAGING (PATHWAYS CONNECT) | | | | | | | | | | | |
| Structural/functional Imaging – s/fMRI | | X | | | | X | | | | X^^ | |
| ONGOING | | | | | | | | | | | |
| ***Adverse events log | | | | | | | | | | | X |
| ***Concomitant medications log | | | | | | | | | | | X |
| Withdrawal form | | | | | | | | | | | X |
| PHARMACY | | | | | | | | | | | |
| Study medication dispensing/administration | | | | | | X | X+++ | X | X+++ | X | |
| Study medication dosing log | | | | | | | | | | | X |

| Timepoint/Event | Screening (≤ 12 weeks to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|

**Legend**

# Not required if already captured as part of PATHWAYS HORIZON
* All ongoing forms to be reviewed and updated at each visit
** Tanner staging assessment at 24 months is optional
***Safety review including vital signs, adverse event reporting, concomitant medication review, pregnancy test (POCBP only) at every injection visit for participants switching to 3-monthly or monthly IMP preparation.
^^^Gender Identity Questionnaire completed only at baseline for Parents
++ People of child bearing potential only
+++ Dispensing at Months 15,21 if changing to 3 monthly preparation
^ Bone age scan at M12 & M24 optional
^^ Visit window for final scan of 6 weeks prior to/following final treatment injection
### Ongoing questionnaires and DEXA scans completed annually during follow up period

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

***Table 6. Schedule of events for HORIZON INTENSIVE participants***

| Timepoint/Event | Screening (Day –XX to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Registration form & consent | X | | | | | | | | | | |
| Eligibility | | X | | | | | | | | | |
| Medical history | X | | | | | | | | | | |
| Demographic data | X | | | | | | | | | | |
| BASELINE CHARACTERISTICS # | | | | | | | | | | | |
| ADHD (SNAP-IV) | | X | | | | | | | | | |
| Autism (SCQ) | | X | | | | | | | | | |
| About Yourself Questionnaire | | X | | | | | | | | | |
| Status form | | | X | X | X | X | X | X | X | X | |
| QUESTIONNAIRES ## | | | | | | | | | | | |
| Quality of Life (KIDSCREEN-10) | | X | | | | X | | | | X | X^ |
| KIDSCREEN-52 – all domains | | X | | | | X | | | | X | X^ |
| Personal priorities | | X | | | | X | | | | X | X^ |
| Gender Identity Questionnaire** | | X | | | | X | | | | X | X^ |
| Social Transition Questionnaire | | X | | | | X | | | | X | X^ |
| Anxiety and depression symptoms (RCADS-25) | | X | X | X | | X | X | X | | X | X^ |
| Suicide/ Self Harm (ASQ) | | X | X | X | | X | X | X | | X | X^ |
| Gender dysphoria (UGDS-GS) | | X | | | | X | | | | X | X^ |
| Body image/ dysphoria (BIS-GS) | | X | | | | X | | | | X | X^ |

| Timepoint/Event | Screening (Day –XX to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Emotional Dysregulation (DERS-18) | | X | | | | X | | | | X | X^ |
| Sexual Attraction Questionnaire | | X | | | | X | | | | X | X^ |
| Romantic Relations (ALSPAC measure) | | X | | | | X | | | | X | X^ |
| Parental support (PAGES) | | X | | | | X | | | | X | X^ |
| Trauma (APCTSS) | | X | | | | X | | | | X | X^ |
| Emotional & Behavioural Problems (CBCL, YSR) | | X | | | | X | | | | X | X^ |
| Eating Problems (SCOFF) | | X | | | | X | | | | X | X^ |
| SCANS | | | | | | | | | | | |
| DEXA | | X | | | | | | | | X | |
| Bone Age X-Ray | | X | | | | | | | | | |
| CLINICAL MEASURES | | | | | | | | | | | |
| Self-reported puberty staging assessment+ | | X | | | | | | | | X | |
| Vital signs | | X | | | | | | | | X | |
| Review of systems (history and examination) | | X | | | | | | | | X | |
| (Optional) Body Composition - Tanita Scale | | X | | | | | | | | X | |
| Safety bloods | | X | | | | | | | | X | |
| Urinalysis | | X | | | | | | | | X | |
| COGNITIVE MEASURES+ | | | | | | | | | | | |
| General Intelligence – WISC V | | X | | | | | | | | X | |
| Inhibition, shifting, verbal fluency – D-KEFS | | X | | | | | | | | X | |
| Memory: visual recognition, verbal recall - CHAMP | | X | | | | | | | | X | |

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

| Timepoint/Event | Screening (Day –XX to Day 0) | Baseline (Day 0) | Month 3 [+/- 2 weeks] | Month 6 [+/- 2 weeks] | Month 9 [+/- 2 weeks] | Month 12 [+/- 4 weeks] | Month 15 [+/- 2 weeks] | Month 18 [+/- 6 weeks] | Month 21 [+/- 2 weeks] | Primary outcome Month 24 [+/- 8 weeks] | Ongoing* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Memory validity profile - MVP | | X | | | | | | | | X | |
| Executive functions at home - BRIEF | | X | | | | | | | | X | |
| MAGNETIC RESONANCE IMAGING (PATHWAYS CONNECT) | | | | | | | | | | | |
| Structural/functional Imaging – s/fMRI | | X | | | | | | | | X^^ | |
| ONGOING | | | | | | | | | | | |
| Adverse events log | | | | | | | | | | | X |
| Concomitant medications log | | | | | | | | | | | X |
| Withdrawal form | | | | | | | | | | | X |

**Legend**

# Not required if already captured as part of PATHWAYS HORIZON
##
* All ongoing forms to be reviewed and updated at each visit
^ Ongoing questionnaires completed annually during funding period
^^ Visit window for final scan of 6 weeks
**Gender Identity Questionnaire completed only at baseline for Parents

# APPENDIX B – Data Flow

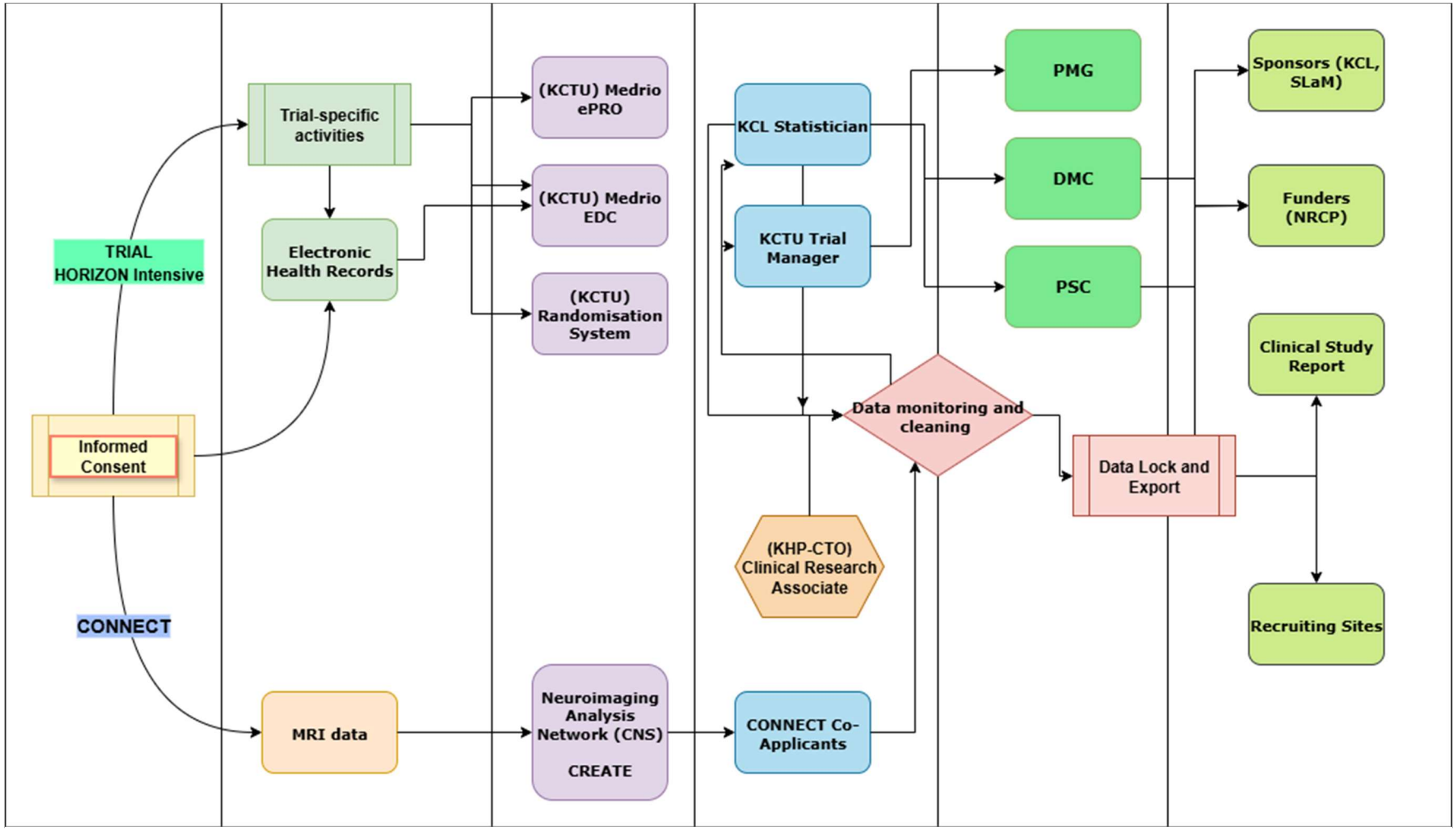
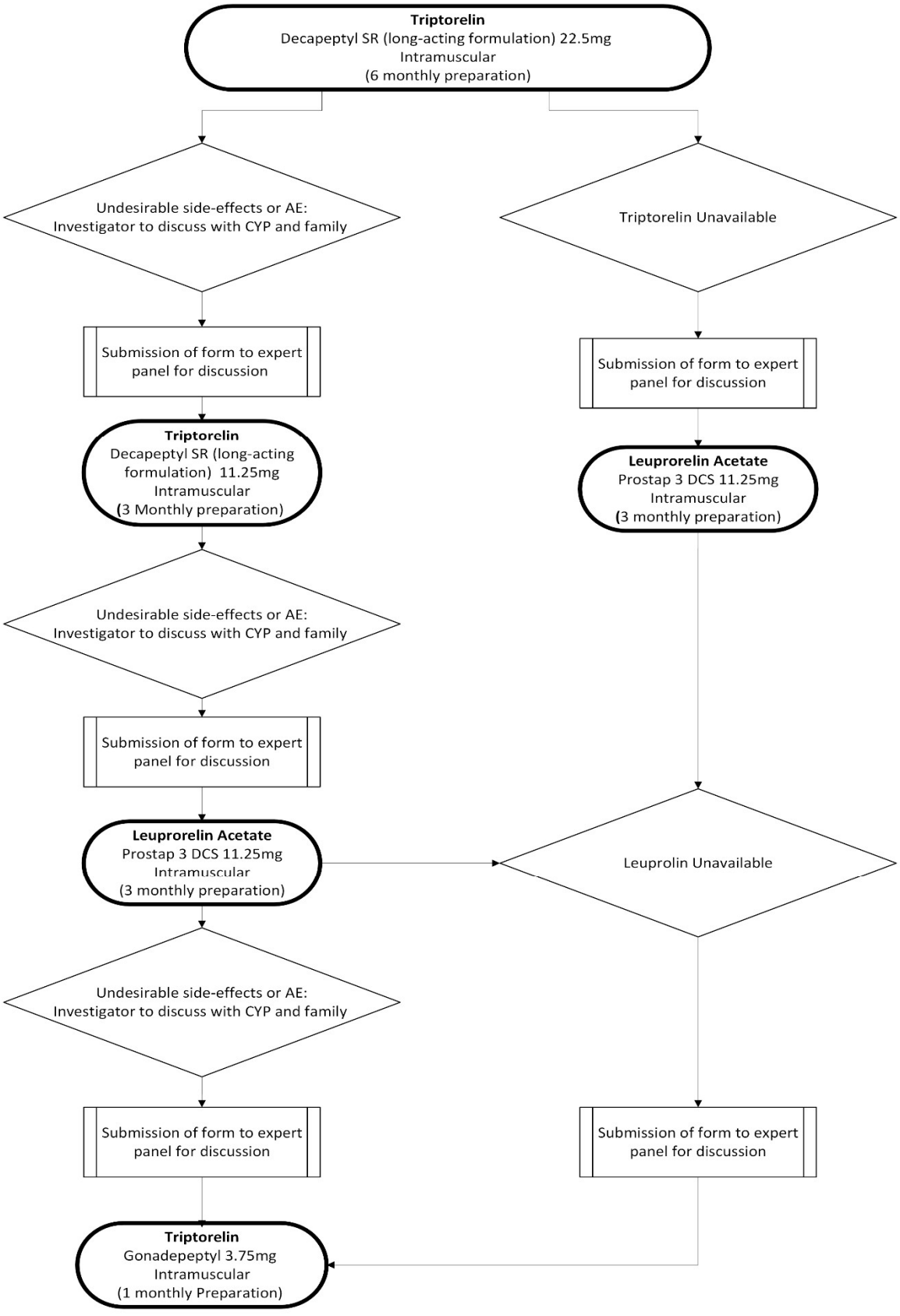



***Figure 3 –*** *A flow diagram depicting the flow of participant data in PATHWAYS TRIAL, HORIZON INTENSIVE, and CONNECT*

The electronic version of this document is the latest version. It is responsibility of the individual to ensure that any paper material is the current version. Printed material is uncontrolled documentation.

# APPENDIX C – Alternate IMP preparation flowchart



# APPENDIX D - Side-effects of alternative GnRHa's

## Leuprorelin Acetate IM

**Common:**

In under 18's: Depression, emotional lability, gastrointestinal discomfort, haemorrhage, headache, metrorrhagia, nausea, skin reactions, vaginal discharge, vomiting.

In adults: decreased appetite, arthralgia, bone pain, breast abnormalities, depression, dizziness, fatigue, gynaecomastia, headache, hepatic disorders, hot flush, hyperhidrosis, insomnia, altered mood, muscle weakness, nausea, paraesthesia, peripheral oedema, sexual dysfunction, testicular atrophy, vulvovaginal dryness, weight change.

**Uncommon or Rare:**

In under 18's: Myalgia

In adults: alopecia, diarrhoea, fever, myalgia, palpitations, visual impairment, vomiting, haemorrhage

**Unknown frequency:**

In under 18's: Idiopathic intracranial hypertension, interstitial lung disease, seizure, severe cutaneous adverse reactions.

In adults: Anaemia, dyslipidaemia, impaired glucose tolerance, hypertension, hypotension, idiopathic intracranial hypertension, insulin resistance, interstitial lung disease, leucopenia, metabolic syndrome, osteoporosis, paralysis, pulmonary embolism, QT prolongation, seizure, severe cutaneous adverse reactions (SCARs), skin reactions, spinal fracture, thrombocytopenia, urinary tract obstruction.

# PATHWAYS Trial Protocol v2.1 20.11.2025 CLEAN_Sig Page

Final Audit Report 2025-11-20

| | |
|---|---|
| Created: | 2025-11-20 |
| By: | KCTU King's Clinical Trials Unit (randomization.request@kcl.ac.uk) |
| Status: | Signed |
| Transaction ID: | CBJCHBCAABAAh9r2DdDlfsZFnoTmEaLRQA-hznnnTpfkn |

## "PATHWAYS Trial Protocol v2.1 20.11.2025 CLEAN_Sig Page" History

Document created by KCTU King's Clinical Trials Unit (randomization.request@kcl.ac.uk)
2025-11-20 - 12:38:23 GMT- IP address: 143.68.145.194

Document emailed to Emily Simonoff (emily.simonoff@kcl.ac.uk) for signature
2025-11-20 - 12:40:11 GMT

Email viewed by Emily Simonoff (emily.simonoff@kcl.ac.uk)
2025-11-20 - 12:46:24 GMT- IP address: 31.126.126.162

Document e-signed by Emily Simonoff (emily.simonoff@kcl.ac.uk)
Signature Date: 2025-11-20 - 12:46:47 GMT - Time Source: server- IP address: 31.126.126.162

Document emailed to michael.absoud@kcl.ac.uk for signature
2025-11-20 - 12:46:48 GMT

Email viewed by michael.absoud@kcl.ac.uk
2025-11-20 - 13:03:54 GMT- IP address: 18.168.47.123

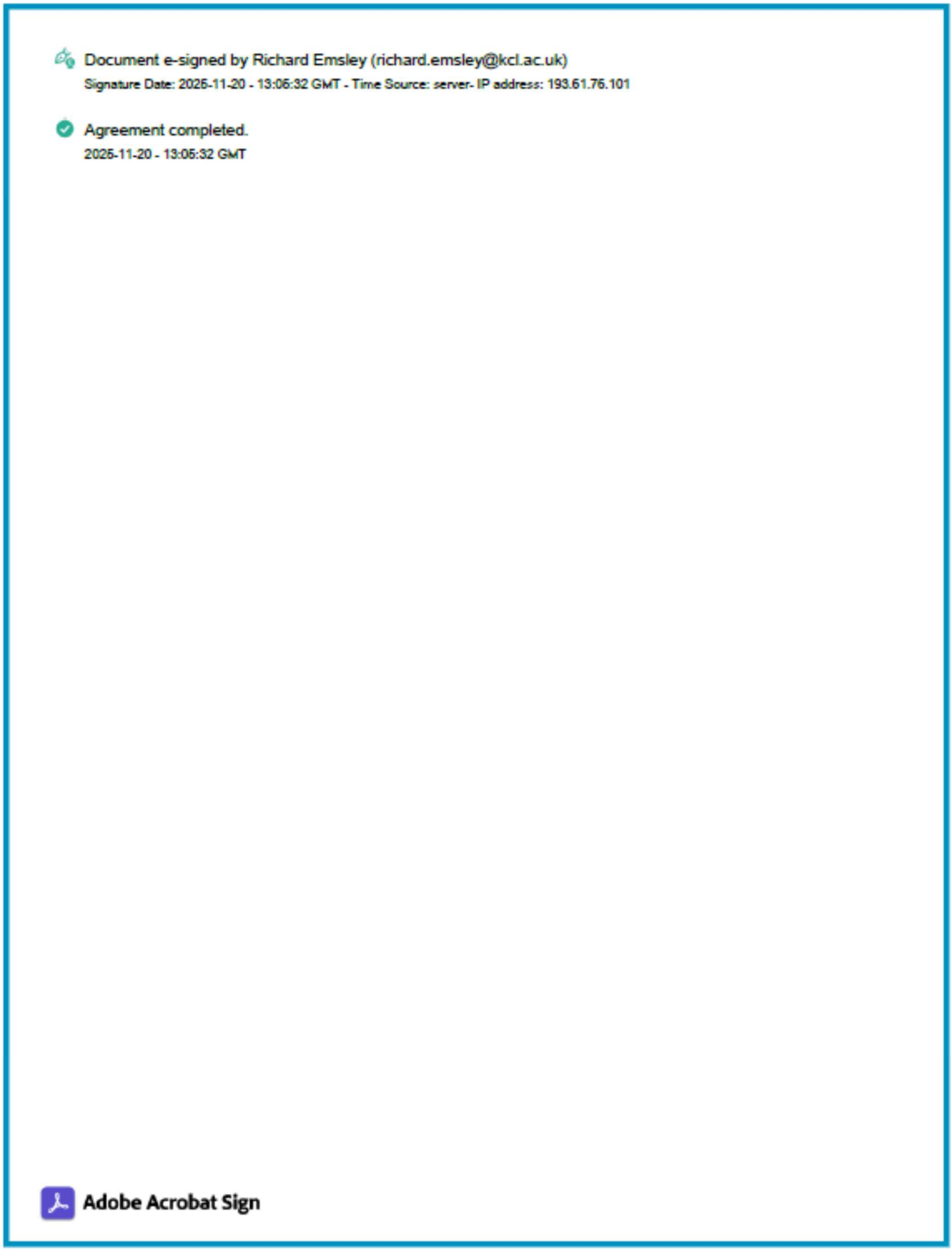
Signer michael.absoud@kcl.ac.uk entered name at signing as Michael Absoud
2025-11-20 - 13:04:43 GMT- IP address: 18.168.47.123

Document e-signed by Michael Absoud (michael.absoud@kcl.ac.uk)
Signature Date: 2025-11-20 - 13:04:46 GMT - Time Source: server- IP address: 18.168.47.123

Document emailed to Richard Emsley (richard.emsley@kcl.ac.uk) for signature
2025-11-20 - 13:04:47 GMT

Email viewed by Richard Emsley (richard.emsley@kcl.ac.uk)
2025-11-20 - 13:05:19 GMT- IP address: 104.47.30.126

Adobe Acrobat Sign


Document e-signed by Richard Emsley (richard.emsley@kcl.ac.uk)
Signature Date: 2025-11-20 - 13:05:32 GMT - Time Source: server- IP address: 193.61.76.101
Agreement completed.
2025-11-20 - 13:05:32 GMT
Adobe Acrobat Sign