Puberty suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS)

PATHWAYS – HORIZON: A longitudinal observational study

Trial Identifiers

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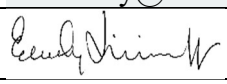
Signature		Date: 20/06/2025

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Study Synopsis

TITLE OF STUDY:	**Puberty suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS).** **PATHWAYS – HORIZON: A longitudinal observational study**
Protocol Short Title/ Acronym:	PATHWAYS-HORIZON
Study Phase:	Longitudinal Observational Cohort Study
Sponsor Name(s):	King's College London and South London and Maudsley NHS Foundation Trust
Chief Investigator(s):	Professor Emily Simonoff Dr Michael Absoud (Deputy CI)
Medical Condition or Disease Under Investigation:	Gender Incongruence
Purpose of Study:	The PATHWAYS HORIZON study aims to address key evidence gaps by reporting on the psychosocial and clinical characteristics of young people referred to the UK CYPGS.
Primary Objective (s):	1) To improve the understanding of the care needs and holistic developmental journeys of all CYP attending NHS Gender Services. 2) To understand how the developmental trajectories and short – to medium-term outcomes of CYP with gender incongruence are influenced by differences amongst CYP and their life experiences.
Secondary Objective(s):	1) To improve understanding of how care options are experienced by CYP and their parents/carers/legal guardians.. 2) To develop a novel interview-based outcome measure that focuses on CYP's aspirations and goals from gender care. 3) To explore similarities and differences in the holistic perspectives of CYP and their parents/carers/legal guardians to gain a comprehensive understanding of how gender incongruence affects CYP.
Trial Design:	Longitudinal observational cohort study
Sample Size:	3600 participants
Summary of Eligibility Criteria:	Inclusion Criteria 1. The CYP has an accepted referral to CYPGS, or has already attended an appointment at a CYPGS. 2. The CYP is awaiting or has received their first appointment with the service at the time of completing baseline measures. 3. Valid assent/consent has been obtained: a) For CYP under the age of 16 at recruitment providing self-reports: i. Parent/legal guardian gives consent for them to participate AND ii. CYP gives assent to participate. CYP is deemed to have capacity to consent by their clinician and gives consent to participate. b) For CYP 16 years and above providing self-report information:

	i. CYP gives consent to participate. OR ii. Personal Consultee gives consent for the CYP to participate if the CYP lacks capacity to consent. c) For parent-reported measures for CYP under the age of 16 at recruitment: Parent/legal guardian consents to their own participation to provide parent-reported measures. d) For parent-reported measures for CYP 16 years and over at recruitment: Parent/legal guardian consents to their own participation to provide parent-reported measures and CYP consents to parent/legal guardian completing measures. Exclusion Criteria 1. CYP did not attend a first appointment at CYPGS. 2. CYP deemed unsuitable in the opinion of the investigator for clinical or other reasons.
Version and Date of Final Protocol:	V1.1 13.06.2025

Revision History

Protocol version	Description of changes from previous revision	Effective Date
Protocol Version 1.0	New Protocol	19.03.2025
Protocol Version 1.1	Informed consent (section 3.3) amended; Inclusion criteria points 3,4,5,6 condensed into one criterion (section 3.2.1); Additional exclusion criterion added (section 3.2.2); Measures/ Data Forms (section 4.4) Primary outcome changed from KIDSCREEN-52 to KIDSCREEN-10; Trauma measure changed from CPSS to APCTSS; new measures Social Transition Questionnaire, Parental 'About Yourself' Questionnaire; validated measures reformatted for online completion and binary language amended to gender neutral language where required; questionnaire items/ response categories added or omitted Annual Health Update, CBCL, YSR, Gender Identity Questionnaire, ASQ, SCOFF, Romantic Relations, Sexual Attraction Questionnaire; DERS-P non-validated version changed to validated version; Gender Identity, ASQ and CPSS no longer clinician supported at baseline; Novel Outcome Measure Development (section 4.8) third interview added to assess sensitivity to change; Data security (section 5.2) updated to reflect change in secure storage facilities for personal data; Adverse event collection process (sections 4.5.1, 6) clarified; Statistical Methods (section 8) updated to reflect changes in measures.	13.06.2025

Glossary of terms

ADHD	Attention-Deficit Hyperactivity Disorder
AE	Adverse Event
ALSPAC	Avon Longitudinal Study of Parents and Children
ASAI	Adolescent Sexual Activity Index
APCTSS	Adolescent Primary Care Traumatic Stress Screen
ASD	Autism Spectrum Disorder
ASQ	Ask Suicide-Screening Questions
BIS-GS	Body Image Scale – Gender Spectrum
CA	Competent Authority
CBCL	Child Behaviour Checklist
CI	Chief Investigator
CRF	Case Report Form
CSV	Comma-Separated Values
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
CYP	Children and young people
CYPGS	Children and Young People Gender Service
DCR	Data Clarification Request
DERS	Difficulties in Emotion Regulation Scale
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcomes
GCP	Good Clinical Practice
GP	General Practitioner
GIH	Gender Incongruence History
GnRHa	Gonadotropin Releasing Hormone Analogues

IOPPN	Institute of Psychiatry, Psychology and Neuroscience
KCL	King's College London
KCTU	King's Clinical Trials Unit
MNAR	Missing Not at Random
NIHR	National Institute for Health and Care Research
NPN	National Provider Network
PAGES	Parental Attitudes of Gender Expansiveness Scale
PI	Principal Investigator
PIN	Participant Identification Number
PIS	Participant Information Sheet
PMG	Programme Management Group
PSC	Programme Steering Committee
PTSD	Post Traumatic Stress Disorder
RA	Regulatory Agency
RCADS	Revised Child Anxiety and Depression Scale
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCQ	Social Communication Questionnaire
SDW	Source Data Worksheets
SDV	Source Data Verification
SNAP-IV	Swanson, Nolan and Pelhan ADHD Rating Scale
TM	Trial Manager
TS	Trial Statistician
UGDS-GS	Utrecht Gender Dysphoria Scale
UK	United Kingdom

PROTOCOL CONTENT

1. Introduction

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. **This protocol is specifically for one component of the research, PATHWAYS HORIZON**, which is a longitudinal observational cohort study. However, this general background section starts with a description of the full programme, in order to understand how HORIZON is situated within the programme, and how participants may move from one study to another.

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].

Until recently, gender incongruence was considered rare [2] with limited clinical awareness and service provision. 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 aims, including 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 [3] reported that 0-8% (including 2% of UK youth [4]) receiving GnRHa desisted from the treatment and a transitioning pathway [3]. This raises concerns about whether the intervention might itself be narrowing rather than increasing perceived choices.

The use of GnRHa became part of routine care in many settings without the standard of rigorous evaluation of benefits and risks, often including randomised clinical trials (RCTs) [3]. The increasing use of GnRHa elicited differing and often polarised views about the optimal treatment pathway for CYP with gender incongruence and specifically about the benefits and safety of GnRHa to suppress puberty. 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 [3-5].

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, a substantial proportion of 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 have requested more objective clinical evidence to guide decision-making in the interests of longer-term positive outcomes.

1.1 *Summary of PATHWAYS Research Programme*

The PATHWAYS research programme plans to include 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 HORIZON, which is 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), or have attended their first appointment.

The overarching aims of the full 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 experiencing gender incongruence 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 inform longer-term follow-up.

1.1.1 *Studies within the PATHWAYS programme*

1.1.1.1 **PATHWAYS HORIZON**

PATHWAYS HORIZON is an observational cohort (n~3600) of all CYP attending the Children and Young Persons Gender service (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).

1.1.1.2 **HORIZON Intensive**

In addition, we will recruit CYP to HORIZON Intensive from the HORIZON cohort who will be broadly matched to those participating in TRIAL, providing a non-randomised comparison group. (Note that “Intensive” refers to research monitoring rather than clinical care.) *The*

PATHWAYS HORIZON Intensive protocol will be included in the PATHWAYS TRIAL protocol and application.

1.1.1.3 **PATHWAYS TRIAL**

PATHWAYS Trial is a trial of GnRHa in the management of gender incongruence in CYP.

1.1.1.4 **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.

1.1.1.5 **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.

1.1.1.6 **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.

1.1.2 *Relationship between PATHWAYS studies*

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 1** depicts the relationship and participant overlap between studies.

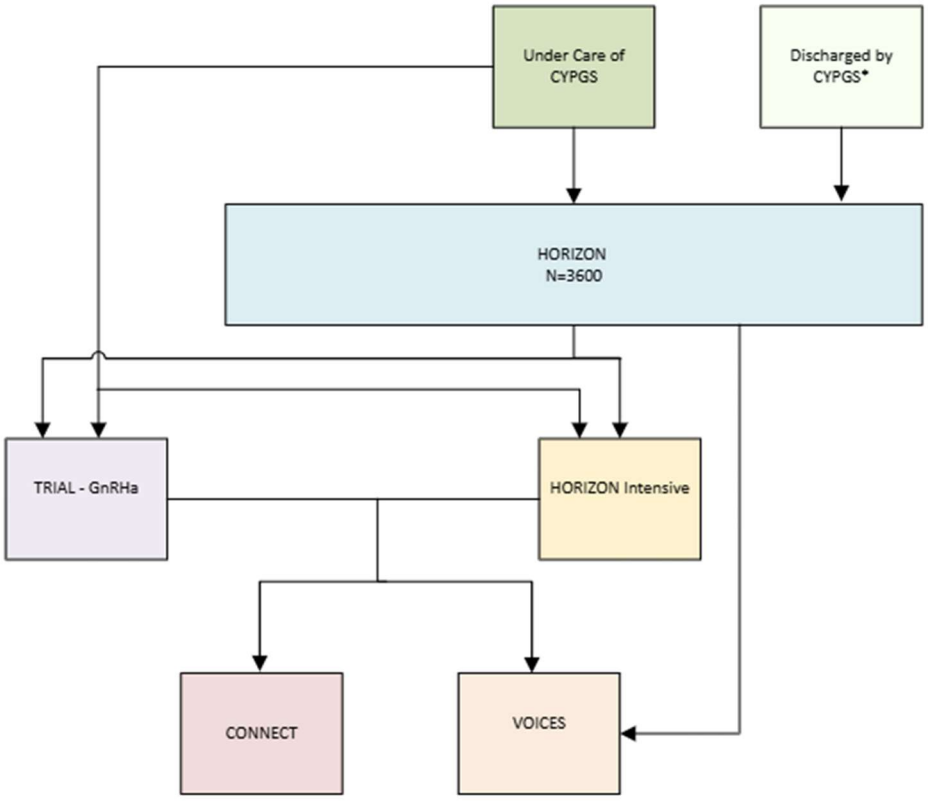

Figure 1 - *Overlap between PATHWAYS participants in different PATHWAYS studies*

1.2 ***Background specific to the PATHWAYS HORIZON Protocol.***

Over the past two decades the number of referrals of young people seeking care in gender services has increased significantly [6-8], with Figure 2 [8] depicting the 20-fold increase in UK referrals between 2000 and 2017 .

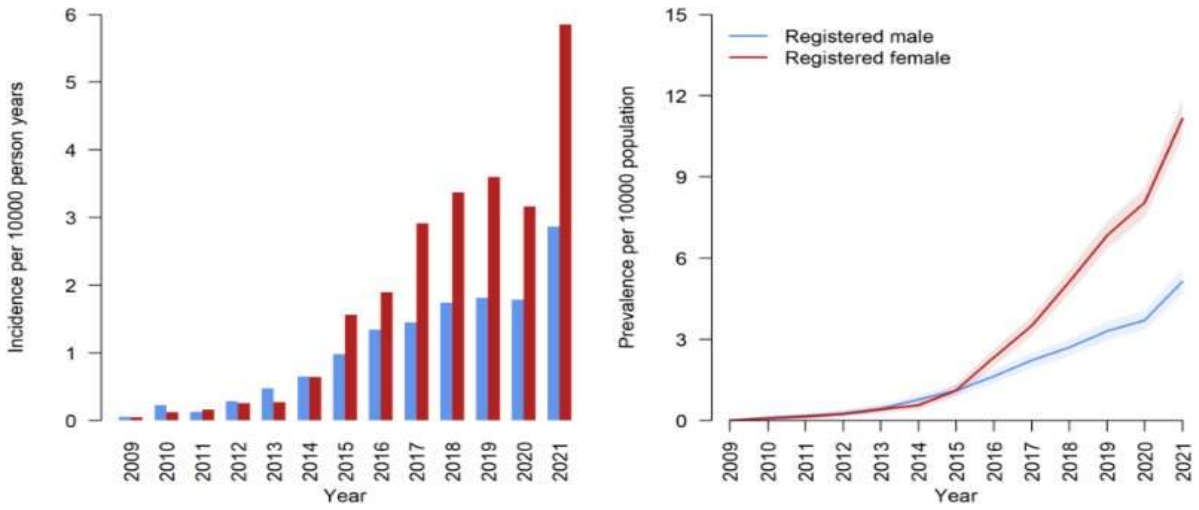

Figure 2. The characteristics of young people seeking support in the United Kingdom (UK) have also changed over this time period. *This means that the results of studies reporting on earlier cohorts of CYP may not apply to those currently accessing gender services.*

These differences include:

(1) Markedly increased rates of birth-registered females, shifting from a preponderance of birth-registered males to birth-registered females [6, 8];
(2) Older age of presentation to gender services [8], which is therefore associated with more advanced pubertal status;
(3) A marked increase in CYP who also have neurodevelopmental conditions, particularly autism and possibly attention-deficit hyperactivity disorder (ADHD) [9, 10]. The reason for this is presently unclear; it is likely that this represents in part improved recognition of these conditions, but also likely represents a true increase in presentation amongst this group of CYP;
(4) Increased additional mental health problems, including anxiety, depression and eating disorders [11, 12];
(5) Substantial rates of adverse childhood experiences that are distressing and, in some instances, may lead to post-traumatic stress disorder (PTSD) [13, 14].

Recent changes in the UK service provision established regional children and young people's gender service hubs, referred to as the CYPGS. Currently three services are in place: the London and Northwest hubs and the Bristol centre, and there are plans for a further three or four centres to open over the next two years. These new services include paediatricians, psychiatrists, psychologists, psychotherapists, speech and language therapists, specialist nurses, and occupational therapists working in multidisciplinary teams. A consistent approach has been agreed across services to provide and record a comprehensive assessment of the full range of needs. This assessment leads to a holistic, individualised formulation of each CYP, which is then shared with the CYP and their parents, leading to agreement on a personalised intervention plan. Where possible, evidence-based interventions will be recommended, but as highlighted above, there is a dearth of evidence for treatment efficacy in this population. Consistency of the approach to care is being developed and monitored by a National Provider Network (NPN). Clinicians delivering care in the new services, alongside scientists, health-service managers and policymakers, want to understand the characteristics of this population, their care needs, and their longitudinal course in relation to gender incongruence, mental and physical health, and quality of life.

The PATHWAYS HORIZON study aims to address these evidence gaps by reporting on the psychosocial and clinical characteristics of young people referred to the UK CYPGS. The study will evaluate a range of characteristics at the time of presentation that may influence management and intervention choices as well as short and longer-term outcomes. PATHWAYS HORIZON will describe outcomes including quality of life, gender identity- and body-dysmorphia-related experiences, mental health, and psychosocial functioning.

2. Study Design

PATHWAYS HORIZON is a longitudinal observational cohort study with an anticipated sample size of approximately 3600 participants (CYP- parent/caregiver dyads). All CYP (and their parents/carers/legal guardians) attending any of the CYPGS will receive information about the study and will be eligible to participate. PATHWAYS HORIZON will run for the duration of the PATHWAYS programme, estimated at 5.5 years. Participants will be recruited into the study for the first 3.5 years. Data will be collected at entry into the service and then on an annual basis until the end of the study. Longer-term follow-up is scientifically important due to the often life-long nature of gender incongruence, and participants will be asked for optional consent to be contacted in the future and for data linkage to health and educational databases. Although participants will be contacted about PATHWAYS HORIZON when they first attend

the CYPGS, they may choose to join the study immediately or later. They can withdraw participation at any time during their attendance in the CYPGS (or afterwards) without affecting their care.

The study will employ a combination of self-report, parent/caregiver-reports and clinician-administered or researcher-supervised scales. Where feasible, the assessments for CYP and their parents/carers/legal guardians should be conducted separately to ensure response validity. Similarly, wherever possible, a 'core' parent informant will be identified, who will be contacted sequentially over time to complete assessments. However, substitution of another parent/caregiver will be allowed within the study protocol.

2.1 ***Objectives***

2.1.1 *Primary Objectives*

1. To improve the understanding of the care needs and holistic developmental journeys of all CYP attending NHS Gender Services.
2. To understand how the developmental trajectories and short – to medium-term outcomes of CYP with gender incongruence are influenced by differences amongst CYP and their life experiences.

2.1.2 *Secondary Objectives*

1. To improve understanding of how care options are experienced by CYP and their parents/carers/legal guardians.
2. To develop a novel interview-based outcome measure that focuses on CYP's aspirations and goals from gender care.
3. To explore similarities and differences in the holistic perspectives of CYP and their parents/carers/legal guardians to gain a comprehensive understanding of how gender incongruence affects CYP.

3. Participants & Recruitment.

3.1 ***Participants***

Participants will include CYP of any age referred to the CYPGS, along with their parent(s), caregiver(s), or legal guardian(s) following acceptance of the referral. CYP may be seen in the service up to age 18 years, at which point they are referred to adult Gender Services. Referrals to the CYPGS may be made by an NHS-commissioned secondary care level paediatric service or CYP mental health service. For a referral to be accepted, it must indicate that the CYP is experiencing concerns or distress related to their gender identity. The absence of a lower age limit applies only to the HORIZON study and not to other studies in PATHWAYS which have a greater focus on GnRHa. The purpose of the HORIZON study is to provide a comprehensive description of the presenting characteristics and developmental trajectories of all CYP presenting to the service, in order to improve care for the entire population.

Only CYP and their parents/carers/legal guardians who attend a first assessment appointment in the CYPGS will be included. CYP remain eligible to participate in the study even after discharge from the services, including those who transition to adult services. All CYP and their parents/carers/legal guardians will be followed up annually, even if they no longer remain within the service and/or have been discharged, unless they withdraw from the study.

CYP and their parents/carers/legal guardians who attended a first appointment in the new CYPGS and were discharged prior to the study onset will also be contacted to provide them with the opportunity to participate.

3.2 *Eligibility criteria*

3.2.1 INCLUSION CRITERIA

1. The CYP has an accepted referral to CYPGS, or has already attended an appointment at a CYPGS.
2. The CYP is awaiting or has received their first appointment with the service at the time of completing baseline measures.
3. Valid assent/consent has been obtained:
    a) For CYP under the age of 16 at recruitment providing self-reports:
        i. Parent/legal guardian gives consent for them to participate AND
        ii. CYP gives assent to participate.CYP is deemed to have capacity to consent by their clinician and gives consent to participate.
    b) For CYP 16 years and above providing self-report information:
        i. CYP gives consent to participate. OR
        ii. Personal Consultee gives consent for the CYP to participate if the CYP lacks capacity to consent.
    c) For parent-reported measures for CYP under the age of 16 at recruitment: Parent/legal guardian consents to their own participation to provide parent-reported measures.
    d) For parent-reported measures for CYP 16 years and over at recruitment: Parent/legal guardian consents to their own participation to provide parent-reported measures and CYP consents to parent/legal guardian completing measures.

3.2.2 EXCLUSION CRITERIA

1. CYP did not attend a first appointment at CYPGS.
2. CYP deemed unsuitable in the opinion of the investigator for clinical or other reasons.

3.3 *Informed consent*

All CYP and their parents/carers/legal guardians attending the CYPGS will receive the participant information sheet (PIS) about the study and will be invited to provide assent/consent electronically via the Medrio eConsent module (see section 5.1.2).

Assent/consent from CYP and parents/legal guardians will be considered semi-independent. That is, a parent may choose to provide information about their CYP, even if that CYP declines to participate by providing self-reports. For CYP under age 16 years, parental consent for them to participate is generally required, but can be given even if the parent decides not to participate themselves. CYP 16 years and over will be asked whether they consent to their parent or another trusted adult completing informant versions of questionnaires.

For CYP who turn 16 years during the study period, consent will be taken prior to or at the next assessment point. Informed assent/consent will be obtained from CYP and parents/legal guardians at baseline before any assessment measures are completed. Assent/consent will be documented electronically, and participants will be assured that their decision to participate (or not) will not affect their access to care or future care pathways. This includes endocrine care and involvement in the randomised controlled trial evaluating gonadotropin releasing hormone analogues (GnRHa), PATHWAYS TRIAL.

Parents/legal guardians of CYP <16 and YP 16 years and older will be contacted by the CYPGS to obtain consent and provide their email addresses for PATHWAYS HORIZON researchers to contact them about the study. The PIS will then be sent to participants with other information about their first appointment. Given the relatively low risk nature of this questionnaire study, after receiving the PIS, participants will have the following options:

1. To assent/consent electronically.
2. To request that a researcher gets in touch to tell them more about the study.
3. To delay the decision until after their first appointment in the CYPGS (and be contacted then to answer any questions).
4. To decline participation.

The process of contacting and obtaining assent/consent is as follows:

1. The health care team will send the CYP and parent/legal guardian an email explaining that the CYPGS is collaborating with PATHWAYS and asking for their consent for the research team to get in touch to tell them about the study ("consent for contact"). This will ordinarily be sent with information about the first appointment but will be sent separately for those who have already attended a first appointment.
2. For those participants who agree to be contacted, the health care team (clinic) will notify the research team who will send the PIS and assent/consent, with their details. They may speak to a researcher in person at the CYPGS, by telephone or MS Teams video call to answer any questions.
3. The health care team at the CYPGS will maintain a screening log of participants contacted and their response. For those not providing consent for contact, their file will be flagged at the first appointment. A member of the health care team will then check whether they have considered the consent for contact and chosen not to consent, whether this had not been considered, or they had neglected to respond (as is the experience in other services operating a consent for research contact policy). An anonymised copy of the screening log containing CYP age at referral, length of time on the waiting list, birth-registered sex, ethnicity, index of multiple deprivation decile, known neurodevelopmental diagnosis and whether a member of the health care team requested the CYP was not contacted/included in the study will be shared with the PATHWAYS HORIZON research team in order to understand selective research uptake.
4. There will be a small number of participants who have previously attended and been discharged from the CYPGS. They will receive the same email regarding consent for contact. If they do not respond, they will receive one phone call from the clinic to check whether they have received and read the letter and to record their preferences. For those consenting to contact, the same procedure will be followed.
5. When the CYP <16 years provides assent but parental consent is lacking, a member of the health care team in the CYPGS will get in touch to remind them that parental consent is required. CYP and parents/carers/legal guardians who have not responded may be contacted by a researcher or clinic administrator to ensure they have received the materials.
6. Informed consent from one parent/legal guardian for CYP under 16 years and consent from CYP 16 years and older will be obtained prior to completion of baseline measures. This consent will be taken separately for CYP self-report and parental report. There is no upper time limit for CYP and their parents/carers/legal guardians to consider participation and they will be encouraged to ask any further questions about the study, including referring to the study website which will develop a section specifically for study participants.
7. It is possible there will be rare instances in which the CYP wishes to participate but the parent/legal guardian does not provide informed consent. In such instances, consideration of the CYP's ability to provide informed consent will be delayed until they have been assessed in the CYPGS. The clinical keyworker or their clinical delegate will be requested to assess the CYP's ability to provide informed consent and to consider any disadvantages for their clinical care if they participate against parent support (e.g., family disharmony). The clinician's opinion regarding the CYP's ability to provide informed consent will be recorded in the clinical notes. If they deem the CYP able to provide consent, they will provide an additional signature on the

consent form. Professionals conducting an assessment will have access to training and consultation from a Consultant Paediatrician or Psychiatrist based in the CYPGS.

Study participation will routinely be recorded in the participant's medical record unless a risk is identified. In such cases, the local risk protocol will be followed, which may lead to CYPGS triggering safeguarding or other referrals as necessary at the local site.

Families with CYP unable to complete the baseline assessments, e.g., due to significant intellectual disability, will still be invited to participate in completing parent-reported and clinician-recorded measures. Families with parents/carers/legal guardians who are unable to complete study questionnaires will still be allowed to participate in the study provided they can provide informed written consent, for the CYP (if less than 16 years) to take part in the study.

The mental capacity assessment as per the Mental Capacity Act involves a two-stage assessment: 1) whether the participant has an impairment of or disturbance to, the functioning of the brain; 2) whether the impairment impacts the participant's ability to make a particular decision (e.g. consent to the research study). A participant will be considered unable to make a particular decision if they are unable to understand the information relevant to the decision; retain the information; use or weigh the information; communicate their decision (by any means). For participants that are unable to consent, the parent or the legal guardian will be invited to be the participant's consultee on their wishes and feelings and whether or not they should take part. Where possible, a second parent will be the consultee, who is not the nominated parental informant for questionnaires, to reduce any possible conflict of interest. The personal consultee will get a Consultee Information Sheet informing them about the study and will complete the Consultee Declaration Form. We will provide the Participant Information Sheet +16 and Easy Read Participant Information Sheet +16, as appropriate.

Only participants who provide informed consent to be contacted regarding future research when consenting to participation in PATHWAYS Horizon will be contacted for the novel outcome measure study. Those contacted will receive the novel outcome measure PIS and will be invited to provide assent/ consent to the following:

1. To participate in the novel outcome measure study through completing an interview and research measures.
2. For information already being collected from routine clinical outcomes and clinical records as part of service evaluation to be included in research data.
3. For long-term follow-up of data linkage to health and education records.
4. To be contacted to arrange an interview.
5. For the interview to be audio recorded for the purposes of data collection.
6. For the CYP's General Practitioner to be informed of their participation in the research.

For a visual representation of the possible consent/assent scenarios in PATHWAYS HORIZON, please refer to the flowchart in Annex 1.

3.4 *Assessments and assessment windows*

Initial data collection for new cases will be at baseline, defined as just before the first appointment, on the day of the first appointment, or within five months of the first appointment. Subsequent data collection will take place annually, with timing related to the initial assessment in the CYPGS. CYP and parents/carers/legal guardians who decline/defer participation at initial contact may join PATHWAYS HORIZON at a later date, which will include baseline characterisation.

3.4.1 *Assessment windows*

Timing of annual assessments will be based on the date of the first assessment in the CYPGS. For all participants, the subsequent annual data collection windows will commence at 6 weeks prior to their annual date and will extend until 5 months after their annual date.

All participants will be contacted via text or email as preferred, 6 weeks prior to their annual date. Participants who do not respond will be contacted again on their annual date. A further reminder will be sent 2 weeks after their annual date for any participants who have not responded, at which point they will also be asked whether they can be contacted directly. If no response has been received after 3 reminders, a member of the research team will follow-up with the participant via phone to offer their assistance. At each point of contact participants will be given the option to withdraw from the study should they no longer wish to participate.

3.4.2 *Completion of assessments*

Participants aged 12 years and older, and their parents/carers/legal guardians are expected to complete the assessments via an online survey platform (ePRO), as a starting point. For children under 12 years and CYP with neurodevelopmental conditions, such as autism, ADHD or intellectual disability, or specific learning disabilities such as dyslexia, those with English as a second language or due to personal preference, assessments may be conducted face-to-face, via video call, or through telephone interviews, depending on participant preference. This will also be offered to those where parents/carers/legal guardians have additional needs or English is not the first language. For these participant groups, where researchers are completing questionnaires directly with participants, they will be instructed to use their discretion in determining whether the informant understands the question and can provide valid responses.

All participants will be informed that a researcher can support them via telephone or video call to complete any assessments. Interpreters may be used as required. Researchers will proactively reach out to participants when the healthcare professionals or administrators in the CYPGS suggests this may be helpful, based on their clinical interactions and knowledge of the participants. These methods aim to support participation and accommodate specific needs. Participants missing a data collection window will be retained in the PATHWAYS HORIZON cohort for future data collection waves unless they withdraw, or the study ends.

4. Data Collection & Data Entry

Event/Form	Domain, information source (see legend)	Baseline	Month 12	Month 24	Annual Follow Up	Ongoing*	Estimated completion time (minutes)
Registration form & consent	R (1)	X					5
Eligibility	R (1)	X					10
Informed consent/ assent	SQ, PQ (1)	X					10
Medical history	D (6)	X					15
Demographic data	D (1)	X					2
ADHD (SNAP-IV)	PQ (5)	X					3
Autism (SCQ)	PQ (5)	X					5
Parental 'About Yourself' Questionnaire	PQ (3)	X					1
Status form	R (1)		X	X	X		1
Quality of Life (KIDSCREEN-52)	SQ, PQ (2)	X	X	X	X		7
Annual health update	SQ, PQ (6) (7)		X	X	X		6
Gender Identity Questionnaire	SQ (3), PQ**(3)	X	X	X	X		1
Social Transition Questionnaire	SQ (3)	X	X	X	X		1
Anxiety and depression symptoms (RCADS-25)	SQ, PQ (4) (7)	X	X	X	X		5
Suicide/ Self Harm (ASQ)	SQ, PQ (4) (7)	X	X	X	X		1
Gender dysphoria (UGDS-GS)	SQ (3)	X	X	X	X		3
Body image/ dysphoria (BIS-GS)	SQ (3)	X	X	X	X		3
Emotional Dysregulation (DERS)	SQ, PQ (4)	X	X	X	X		3
Sexual Attraction Questionnaire	SQ (3)	X	X	X	X		1
Romantic Relations (ALSPAC measure)	SQ (3)	X	X	X	X		5
Parental support (PAGES)	SQ, PQ (4)	X	X	X	X		3
Trauma (APCTSS)	SQ, PQ (4)	X	X	X	X		2
Emotional & Behavioural Problems (CBCL, YSR)	SQ, PQ (4)	X	X	X	X		15
Eating Problems (SCOFF)	SQ, PQ (4)	X	X	X	X		1
Withdrawal form	R (1)					X	2

LEGEND
Domains:
1=protocol adherence; 2= personal priorities and quality of life; 3= gender; 4=mental health; 5= neurodevelopmental difference; 6=physical health; 7=adverse events
Information source:
R=researcher-completed; SQ=self-reported questionnaire; PQ=parent-reported questionnaire; PQ**= parent reported questionnaire at baseline only, D=direct observation/examination

TABLE 1 SCHEDULE OF EVENTS
** All ongoing forms to be reviewed and updated at each visit.*

4.1.1 *Enrolment visit*

Participants may enrol electronically or in person, providing e-consent. Enrolment for CYP-reported measures is considered complete when there is (1) valid consent from CYP 16 years or older (2) valid consent from a parent/legal guardian of CYP under 16 years and CYP assent or (3) valid consent from a CYP under 16 years where deemed to have capacity to consent by their clinician or 4) valid consent from a Personal Consultee where CYP 16 years or older lacks capacity to consent.

4.1.2 *Baseline measures*

These will follow the measures indicated in the Schedule of Events.

4.1.3 *Annual follow-up visits*

Follow up data will be collected as per the Schedule of Events in Table 1 above for the relevant yearly visit and ongoing section. At each follow up timepoint, a status form is completed in the study database to indicate whether the participant remains in the CYPGS.

4.2 DATA ENTRY

4.2.1 *Medrio EDC*

Authorised staff at sites will transcribe baseline and follow up participant data from source data worksheets (SDWs) to the Medrio Electronic Data Capture (EDC) system by going to www.ctu.co.uk and clicking the link to access Medrio. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Study site staff will be delegated by the site PI to access the EDC system via a Study Site Delegation Log. The request for user access must go to the Trial Manager (TM), who will submit user requests for all sites to the KCTU team upon receipt of completed Study Site Delegation Logs. Requests for user access will be processed within a maximum of 5 working days.

Training videos for site data entry staff, site monitors and trial co-ordinators are available at www.ctu.co.uk under the 'Training' section. Users can self-register and should select the Medrio related training videos.

4.2.2 *Medrio eConsent*

The Medrio electronic consent (eConsent) module will be used by site staff to document informed assent/consent from participants and parents/carers/legal guardians.

4.2.3 *Medio ePRO*

The electronic patient reported outcomes (ePRO) module of Medrio will be used by participants to complete self-reported and parent-reported measures outlined in the Schedule of Events above. Participants will be set up on the ePRO module following informed consent.

4.3 DATA COLLECTION

Participant self-report measures should ideally be completed independently, as indicated in the instructions to participants at the top of each measure on ePRO.

Please refer to Annex 2 for individual schedule of events for CYP participants, parent participants, and clinician/researcher collected information.

4.3.1 REGISTRATION FORM AND CONSENT

Upon the participant being added into Medrio EDC, the system will assign a unique study PIN to be used for the participant throughout the study. When valid informed consent has been provided

via the Medrio eConsent module (see section 5.1.2), the study site staff will complete the Registration Form for the participant in the Medrio EDC system using participant initials, date of birth, date of consent, and version number of the assent/consent form.

4.3.2 ELIGIBILITY

CRF confirms the CYP has been offered/attended initial assessment appointment at a CYPGS and their informed assent/consent has been obtained. This will include the date of referral to the CYPGS, date referral accepted, date of first appointment, CYPGS for care confirmation that first appointment attended. The form will also indicate any special procedures to be followed, e.g., if self/parent-report measures should be completed by the researcher. It will designate adults with parental responsibility for CYP under 16 years.

4.4 MEASURES/DATA FORMS

All validated measures where applicable have been adapted for digital use and display

4.4.1 *Baseline only*

4.4.1.1 **Medical history**

At the initial assessment in the CYPGS as part of routine care, clinicians will obtain structured information on participants' medical history as per the domains outlined below. For research sites using the clinical record system EPIC, this will form part of the electronic patient record, which can be extracted and transcribed into the study database. For research sites not using EPIC, a Source Data Worksheet (SDW) will be provided to capture the relevant information.

Medical History Domains:

1. Family Context
2. Developmental History
3. Physical Health
4. Mental Health and Risk
5. Adverse childhood experiences
6. Safeguarding
7. Gender Development and Experiences
8. Sexual Development, Knowledge and Sexual Orientation
9. Education, Peer Relationships, and Social Context
10. Additional Information. Clinical Judgements – Impact assessments and clinical evaluation for various aspects of the CYP's development and wellbeing; Parental Support – Judgements on the level of positive parental support and any conflicts between parents/carers/legal guardians or between parents/carers/legal guardians and the CYP.

4.4.1.2 **Demographics**

This form will include participant date of birth, country of birth, participant ethnicity, participant address with full post code, parental marital status and parents/carers/legal guardians with whom participant is living. Only the date of birth and ethnicity will be entered into Medrio EDC.
(Note for clarity, this is different from the Registration form described above.)

4.4.1.3 **Swanson, Nolan, and Pelham-IV (SNAP-IV)**

The SNAP-IV[15] is an 18-item scale used to assess symptoms of ADHD, across two subscales: inattention and hyperactivity/ impulsivity. Parents/carers/legal guardians 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.

4.4.1.4 **Parental 'About Yourself' Questionnaire**

The 'About Yourself 'questionnaire is a non-validated 2-item self-report measure evaluating gender identity and sex assigned at birth of the parent; these were based on questions from the UK based National LGTB Survey [16]. The Parent will be asked 'Do you identify' as: 'woman/girl', 'man/boy', 'transwoman/transgirl', 'transman/transboy', 'non-binary/genderqueer/agender/gender fluid', 'don't know', 'prefer not to say', 'other'. The second question asks; 'What was your sex assigned at birth?', with response categories of 'female', 'male', 'don't know', and 'prefer not to say'. This will be measured at baseline only. Duration: 1 minute.

4.4.1.5 **Social Communication Questionnaire (SCQ)**

The SCQ is a screening tool used to assess traits of autism spectrum disorder (ASD)[17]. The SCQ current version measures symptoms over the previous 3-months. The measure comprises 40 yes/no questions and will be completed by parents/carers/legal guardians only. Total scores range between 0 and 39, and a clinical cut-off of 15 is used to detect probable ASD. The measure has been adapted to include gender neutral language. Duration: 5 minutes.

4.4.2 ***Longitudinal/outcome -baseline and annual follow-up assessments***

Where possible scales should be completed in the order as they are listed below.

4.4.2.1 **KIDSCREEN-10 (PRIMARY OUTCOME)**

The KIDSCREEN-10[18] 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 described below. Primary outcome scores will be obtained separately, using the single factor structure of the KIDSCREEN-10.

4.4.2.2 **KIDSCREEN-52**

The KIDSCREEN-52 [18] 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 earning, 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 wellbeing. Both a self-report version for CYP and a parent-report version will be administered. The parent-report measure has been adapted to include gender neutral language. Duration: 7 minutes.

4.4.2.3 **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 the gender that someone feels and knows themselves to be. 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', 'in the middle', '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? (select all that apply), 'cisgender', transgender', 'non-binary', 'agender', 'genderfluid', 'genderqueer', 'two-spirit' and 'other'. Duration: 1 minute.

4.4.2.4 **Social Transition Questionnaire**

The Social Transition Questionnaire is a single-item, novel, self-report measure designed to assess the extent to which participants have socially transitioned across different everyday settings. Social transition refers to changes in presentation, such as appearance, clothing, name, or behaviour, that align more closely with an individual's experienced gender. 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.

4.4.2.5 **Adolescent Primary Care Traumatic Stress Screen (APCTSS)**

The APCTSS[19] 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 probably PTSD. A non-validated parent report version has been designed to be a direct comparison of the CYP self-report. Duration: 2 minutes.

4.4.2.6 **Revised Child Anxiety and Depression Scale (RCADS)**

The RCADS-25 [20] 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.

4.4.2.7 **Child Behaviour Checklist (CBCL), Youth Self-Report (YSR)**

The CBCL [21] is an 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.

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

The UGDS-GS [22] 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.

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

The BIS-GS [23] is a gender neutral version of the Body Image Scale (BIS)[24] used to assess an individual's relationship with their body. The scale consists of 33 items. Respondents rate their feelings towards each body part 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. Each item includes a 'don't have' response if the individual does not have that body part (e.g. vagina). Respondents are then asked to rate how they feel about not having that body part using the same 5-point Likert scale, and to indicate whether they would want to change this. Higher scores indicate greater body dissatisfaction. Only CYP self-report versions will be obtained. Duration: 3 minutes.

4.4.2.10 **Ask Suicide-Screening Questions (ASQ)**

The ASQ is a brief 4-item instrument used to assess risk of suicide [25]; 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. We will administer CYP self-report and parent-report versions at baseline and follow-up. 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.

4.4.2.11 **SCOFF Questionnaire**

The SCOFF is a 5-item screening tool designed to identify the core symptoms of anorexia nervosa or bulimia nervosa[26]. 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.

4.4.2.12 **Difficulties in Emotion Regulation Scale (DERS)**

CYP will complete the short version of the Difficulties in Emotion Regulation Scale (DERS-18), which consists of 18 self-report items measuring emotional difficulties [27]. 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 [28]. The 29-item DERS-P[29] 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.

4.4.2.13 **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.

4.4.2.14 **Romantic Relations**

Young people aged 12 and above will complete the ALSPAC Romantic Relations [30] measure, which assesses whether young people have engaged in any of the 14 sexual behaviours from the Adolescent Sexual Activities Index (ASAI) [31], and the sex of the person with whom they did. Items are scored 0= they have not engaged in that sexual activitity, 1= they engaged in that sexual activitity 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.

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

The PAGES-Y[32] 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[33] 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.

4.4.3 ***Annual follow-up timepoints only***

4.4.3.1 **Annual health update**

A questionnaire was designed to assess the CYP's current height and weight, current prescribed medications and diagnoses including neurodevelopmental, mental health and physical health, received in the past year. The questionnaire also assesses the number of GP appointments, planned surgeries or procedures, A&E attendances, or other unplanned admissions in the past year. The reasons for the GP appointments and A&E attendances will be elicited. The length of hospital admission for planned surgeries or procedures and admissions following an A&E attendance will also be measured. At follow-up, parents/carers/legal guardians of CYP under 16 will be sent this questionnaire and asked to complete it with their CYP. Self-report questionnaires will only be obtained from young people aged 16 and above. Duration: 6 minutes.

4.4.3.2 **Status Form**

At each follow up timepoint, a status form is completed to document the participants' status in the study.

4.5 ***Safety data***

4.5.1 ***Adverse events***

The measures included at each assessment point (domain 7 – adverse events) will assess several adverse events (AE) experienced by the CYP since the last assessment. For this study, these will include suicidal thoughts and behaviour (captured by the ASQ), a marked increase in the severity of anxiety or depression symptoms (captured by the RCADS), A&E attendances due to mental health, and any unplanned hospital admissions (captured by the Annual Health Update). Mental distress requiring unplanned hospital admission (captured by the annual health update as any mental health related A&E admission) will be recorded as a serious adverse event (SAE) and will be reported to the CYP's lead clinician or care coordinator at the CYPGS, or their GP. The total duration of hospital admission will be recorded.

4.6 ***Ongoing***

4.6.1 ***Withdrawal***

CYP and or their parents/carers/legal guardians may withdraw from HORIZON at any time, without giving a reason why and without affecting their care in the CYPGS. This includes all forms of intervention that may be offered by the CYPGS. *Specifically, CYP may withdraw from HORIZON without affecting consideration of GnRHa and inclusion in PATHWAYS TRIAL.*

If a CYP chooses to withdraw, they will be asked whether they assent/consent to their parent continuing to participate in HORIZON. Missing data at individual waves will not in itself constitute withdrawal unless the participant has explicitly so indicated.

A withdrawal form must be completed for each participant (CYP and/or parent) choosing to withdraw. A withdrawal form must be completed in the event of CYP death.

4.6.2 ***Change of parent***

It will be possible for a new parent/ caregiver/ legal guardian to complete informant reports in the event that a parent/ caregiver/ legal guardian no longer wishes to participate or in the event of their death.

Should the informant change, a change of parent form will be completed, and separate consent will be obtained from the new informant. A withdrawal form will only be completed for the informant when consent for both parent and CYP is formally withdrawn.

4.7 ***Measures to promote participant retention***

Honorarium: CYP and parent/carer/legal guardian completing informant measures will each receive shop vouchers worth £20 for each data collection episode, regardless of whether they have completed the assessment measures independently or with researcher support.

Researchers will send a newsletter to HORIZON participants at a minimum of twice annually. This will include news about the study and will provide an opportunity for participants to share their own news and accomplishments, if they wish.

4.8 *DEVELOPMENT OF AN INTERVIEW-BASED NOVEL OUTCOME MEASURE FOCUSING ON YOUNG PEOPLE'S GOALS FROM THERAPY*

We will co-develop with our advisory boards, as well as CYP attending the CYPGS and their parents/carers/legal guardians a new, bespoke interview outcome measure. This will be undertaken in year 1 of the study. Our previous focus groups with CYP and parents/carers/legal guardians from the Youth Advisory Forum highlighted the diversity of desired outcomes from gender-affirming care, a finding supported by clinicians' experiences in the Gender Service. Hence, we include a wide range of outcome measures to ensure comprehensive coverage. However, within the population of CYP experiencing gender incongruence, there is currently a poor understanding of which outcomes they wish to be altered through gender-affirming care. When this uncertainty is coupled with the lack of high-quality evidence for a range of therapeutic outcomes for young people, it limits the clinicians' ability to provide targeted information to assist decision-making. To address the question of individual preferences, we will ask CYP and their parents/carers/legal guardians to provide relative weightings for each of the beneficial and negative outcomes identified.

<u>Development</u>
The development phase will commence with a rapid literature review to identify a full set of items for consideration and response categories. (a) Specific consideration will be given to those that have been used in previous studies of gender incongruence (b) coverage of all domains identified by CYP and their parents/carers/legal guardians are important (c) items and response categories that can be objectified, e.g., with frequencies of occurrence or other anchor points and (d) items/response categories that are appropriate for the full age range of the study population, which will be 12-18 years at endpoint.

Following the review, response categories/domains and anchor points will be selected in consultation focus groups with our young adult and parent Advisory Boards, gender care health professionals and CYP without gender incongruence drawn from the general population. Two parallel versions (CYP and parent) will be evaluated by these groups for face and content validity of the items, clarity of probes, appropriateness of anchor points and also to establish any domains/items not highlighted in the literature.

<u>Field Testing</u>
Field testing of the pilot interview will be undertaken among: CYP attending the CYPGS but not considered eligible for the PATHWAYS Trial; CYP not seeking GnRHa through puberty and are no longer eligible for puberty suppression; CYP who have already received GnRHa. We will recruit 75 CYP-parent dyads to complete two independent interviews, no more than one month apart. These interviews will be offered online or in person and will be audio-recorded and re-rated by a second researcher. The interview topic guide will include questions related to the core domains assessed in the KIDSCREEN-52, as well as other domains identified in the literature and by the young adult and parent Advisory Boards.

On the first interview occasion, participants will also be asked to complete key study questionnaire outcome measures (KIDSCREEN, RCADS, BIS-GS, UGDS-GS, CBC-L/YSR). This will provide

a psychometric dataset for test-retest and inter-rater reliability, CYP-parent agreement and convergent and discriminant validity.

Finally, using an online questionnaire of all domains, CYP and parents/carers/legal guardians will be asked to order a complete list of the domains to represent their personal priorities. For younger CYP and CYP/parents/carers/legal guardians with learning difficulties, the task can be supported by a researcher. This task will be completed on the first interview occasion alongside the key study questionnaire outcomes measures.

A purposive sample of 70 CYP-parent dyads will be invited to participate in a third interview 6-months after their baseline interview, in order to test the novel outcome measure's sensitivity to change.

Initial interviews and questionnaire completion will take 90-120 minutes and re-test interviews 60 minutes. Participants will be reimbursed £30 and £20 respectively for each session.

Please refer to Annex 2 (table 5) for the novel outcome measure schedule of events.

5. DATA MANAGEMENT

5.1 DATA MANAGEMENT

The Medrio EDC system dataset, which includes data from the Medrio ePRO module, forms the dataset for the study. The CI will act as custodian for the trial data.

5.1.1 *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.

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.

SDWs will be supplied to all recruiting sites by the TM. These will be prepared after the database specification is finalised and database testing is complete. Participating Sites will complete source data location lists defining the source data at their site.

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.

5.1.2 *Medrio eConsent*

The web based Medrio EDC system will include eConsent (electronic consent).

It is the responsibility of the recruiting site staff to ensure participant identification is verified and documented, and that the participant has had the opportunity to have any questions answered. Recruiting site staff should ensure a copy of the completed consent is provided to the participant and that there is written documentation to evidence this. A copy should also be saved in the Investigator Site File (ISF).

Completing eConsent
Authorised staff will log in to their Medrio EDC account and 'Add' the participant.
There are 2 options for eConsent activation & completion as described below:

1. Remote Completion by Participant (e.g., at home completion):
   For 'Remote' completion (e.g., completion on a computer/smartphone/tablet at home), staff member will enter the participant email address when adding the participant in the EDC.
   A 'Set up Profile' email will be automatically sent to the participant with a link to set up their Medrio Profile and create a password.
   A 'Consent' email will be automatically sent alongside this with a link to their Medrio Profile containing the eConsent document for review and signature.
   Where multiple signatures are required (e.g., Parent & Child), the staff member will need to ACTIVATE REMOTE eConsent within the EDC. The participants will receive a notification each with a link to their Medrio Profile containing the eConsent document for review and signature.

2. In Clinic completion by Participant:
   Authorised staff can LAUNCH the eConsent document within the EDC and hand the computer/smartphone/tablet to the participant for completion at the clinic visit.
   Where multiple signatures are required (e.g., Parent & Child), In Clinic completion is not possible.

eConsent co-signing by Staff and completing Registration
Once participant signature is complete, an authorised staff member will log in to their Medrio EDC account to review correct completion by the participant, co-sign the eConsent and provide a copy to the participant.
Next, the staff member can complete the participant Registration in the EDC so that remaining data can be completed as necessary.

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

Participant Self Report Data (ePRO) Oversight
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.

Participant Withdrawal
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.

Data Entry Guidance for Participant Self Report Data (ePRO)

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

5.2 DATA SECURITY

All applicable statutory requirements and mandatory codes of practice in respect of confidentiality (including, where applicable, medical confidentiality) in relation to such research subjects or their legal guardians.

Data Management Plans will be provided to the TM and documented in the TMF, detailing relevant security information about the data system. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords 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 and a request for access to be revoked must be requested when staff members leave the project.

Participant intials, date of birth and ethnicity will be entered into the Medrio EDC system. No more identifiable data will be entered into the Medrio EDC system. Trial sites will maintain a master participant log linking participant identifiers to Participant Identification Numbers (PINs).

Only participant email address and site can be entered in the EDC before participant has signed a consent form to participate in the trial (as this triggers the eConsent process). No further data will be entered in the EDC unless consent is signed by the participant and authorised staff member. The Medrio eConsent does not form part of the exported dataset for the study.

A link back document for participant information including contact details (study PIN, full name, NHS number, address, email, telephone) will be uploaded to the KCL CREATE Trusted Research Environment (TRE) by the Research Associates attached to each NHS Gender Clinic, for the purposes of contacting participants for follow up data if unresponsive to Medrio ePRO automated data requests. No identifiable data will be held outside theTRE.

5.3 DATA QUALITY PROCESSES

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.
Site staff will respond to Data Clarification Requests (DCRs) within the EDC as required. No data will be amended independently of the study site responsible for entering the data. The KCTU will provide the study team with a Data Management Plan for Medrio EDC which will be filed in the Trial Master File (TMF).

5.4 DATABASE LOCK

At the end of the trial, the site PI's 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 TM will confirm all checks are complete and all data 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 staff 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 following completion of statistical analyses, KCTU will provide a copy of the final exported raw 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 TM will request that all user access is removed from the Medrio EDC system. A copy of the final dataset, analysis dataset and code will be stored in the TMF at the end of the study.

5.5 *Data Monitoring*

Data collected by this study will be taken to a Data Monitoring Committee (DMC). As this is not a trial, the data shall only be given to the committtee for further information on their whole overview of the PATHWAYS programme rather than for the committee to give recommendations based on the data accrued, as would be in a randomised controlled trial.

Data taken to the committee will consist of AEs, Serious AEs (SAEs) and outcome data by timepoint, as it accrues. Adverse events and serious adverse events are collected differently and less comprehensively in this study as opposed to how they would be in an RCT. This will be made clear in the reports to the DMC.

To begin with, data from this study will be taken to the DMC on a yearly basis. This is due to follow-ups being at yearly intervals for participants. This timeline may be altered at the discretion of the DMC if they feel they need to see the data more often.

6. ADVERSE EVENT MANAGEMENT AND REPORTING

Adverse events (AEs) will be recorded based on specific items endorsed by either the CYP or parent/ caregiver in the questionnaires as outlined in section 4.5.1 and the PATHWAYS HORIZON distress protocol, including the ASQ, Annual Health Update and RCADS-25.

Any SAEs occurring to research participants will be reported to the main REC (the REC that gave favourable opinion of the study) within 15 days of the Chief Investigator becoming aware of the event, or the Deputy Chief Investigator in the Chief Investiagtor's absence.

The up to date SAE report form for non-CTIMPs available from the HRA website will be used for this indication.

Based on the data that are being collected AEs will include:

1. Depression or anxiety scores with a T score ≥80 on annual questionnaires when they previously were not (RCADS)
2. Suicidal thoughts and behaviours (ASQ)
3. Unplanned A&E attendances for mental health (Annual Health Update)
4. Unplanned hospital admission for any reason other than mental health (Annual Health Update)

SAEs will be recorded when:

1. Unplanned hospital admission for mental health (Annual Health Update)

Standard safeguarding procedures will be followed if a CYP or parent endorses the questionnaire item relating to an unplanned hospital admission for mental health (SAE). All PATHWAYS researchers who have access to the research database or direct contact with research participants will have level 3 safeguarding training. The PATHWAYS research team also consists of two senior clinical academics with longstanding experience of managing safeguarding concerns, who will be available daily to advise on any safeguarding concerns.

7. ETHICS APPROVAL

Prior to the start of the study, a favourable opinion will be sought from a Research Ethics Committee (REC) for the study protocol, PIS, informed consent form and related documents. The CI will be responsible for preparing the submission packs for REC and Health Research Authority (HRA) approval.

Individual participants will consent to participate. The trial will be conducted in compliance with the Declaration of Helsinki (1996) [34], the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements.

The CI is responsible for submitting an end of study declaration to the REC, defined as completion of all data collection. The CI will submit a final report to the REC and study sponsors with the results, including any publications/abstracts, at the conclusion of the trial within the timelines defined in the regulations. In the event the study is ended prematurely, the CI will notify the REC, citing the reasons for the premature termination.

7.1 *PROTOCOL AMENDMENTS AND VERSION CONTROL OF STUDY DOCUMENTS*

The TM will be responsible for preparing and submitting protocol amendments to the REC. Participant facing documents (e.g. PIS, consent form) will be prepared by the co-ordinating centre (KCTU) and the co-ordinating centre is responsible for maintaining version control.
All correspondence, including submission packs with attachments and approvals, will be filed in the TMF. Recruiting study sites are responsible for communicating relevant approved information to participants.

The TM will be responsible for updating the ISRCTN registry following relevant protocol amendments.

7.2 *POTENTIAL RISK OR* HARM TO STUDY PARTICIPANTS

The PATHWAYS-HORIZON study has identified potential risks and burdens for participants and has implemented measures to minimise them. The study aims to balance these risks with the potential benefits, ensuring that participants' well-being is prioritised throughout the research process.

Participants may experience emotional distress when discussing sensitive topics related to gender incongruence, mental health, and personal experiences. All participants will be given information about voluntary sector organisations offering urgent mental health advice and they will be informed they can pause or stop the study at any time. Participants will also be asked whether they would like a researcher to contact them to discuss their participation should they feel distressed or want further support. Researchers will be trained to handle sensitive topics with care and empathy.

Participation in the study will require time and effort, including completing questionnaires and attending interviews, which could be seen as intrusive or inconvenient. The study will aim to minimise intrusion by aligning research sessions with routine clinic assessments and integrating research activities into participants' existing routines as much as possible. Flexible scheduling and the option to complete assessments online or via telephone will be provided to accommodate participants' preferences and reduce inconvenience. Participants will be given ample notice of appointments and assessments, and efforts will be made to minimise disruption to their daily lives.

As is the case for any study, there is a small potential risk of breach of confidentiality, which could lead to unintended disclosure of personal information. All participant data will be pseudonymised and separated from identifying information after data collection. Unique identification codes will be used and access to personal data will be restricted to authorised members of the research and clinical teams. Strict data protection protocols will be followed to ensure confidentiality, and a data safe haven (see section 5.2) will be used to store participant contact details.

Participants, especially those with limited English proficiency, may misunderstand the study's purpose, procedures, or their rights. Information will be provided in clear, accessible language, and interpreters will be available as needed. Researchers will ensure that participants fully understand the study before obtaining assent/consent.

7.2.1 *Assessment and management of risk*

Responses to questionnaire items that indicate safeguarding risk will be routinely monitored and standard safeguarding procedures will be followed. The CYP's clinician at the CYPGS will be informed should a participant disclose that they have experienced significant distress requiring a hospital admission. If they are no longer open to the CYPGS, then their GP may be informed, as appropriate.

It is explained clearly in the information sheet that should the research team have concerns about a CYP's safety or wellbeing, the research team may discuss this with the CYP's clinical team in the CYPGS or their GP.

Any issues raised that reach the threshold of needing to contact the young person/ parent will be discussed with one of the clinical investigators, all of whom have up to date safeguarding level 3 training. The study team have a clear protocol for recording concerns.

8. STATISTICAL METHODS

8.1 PRIMARY OUTCOME

The primary outcome for the PATHWAYS-HORIZON study is the mental health status and wellbeing of children referred to national gender services for young people in the UK. This will be measured using the CYP self-report version of the KIDSCREEN-10 [23] questionnaire, which evaluates quality of life across ten dimensions.

8.2 SECONDARY OUTCOMES

Secondary outcomes can be split into smaller subcategories. All outcomes are marked as to whether they are continuous, binary, time-to-event or will only be displayed descriptively.
Scales of gender-related distress, mental health symptoms and physical health measures:

- Utrecht Gender Dysphoria Scale – Gender Spectrum (UGDS-GS), continuous
- Revised Children's Anxiety and Depression Scale (RCADS), continuous
- Body Image Scale – Gender Spectrum (BIS-GS), continuous
- Parental Attitudes of Gender Expansiveness Scale for Youth (PAGES), continuous
- SCOFF questionnaire, binary
- Sexual attraction questionnaire, descriptive only
- Adolescent Primary Care Traumatic Stress Screen (APCTSS), continuous
- Romantic Relations questionnaire, descriptive only
- Gender identity question, descriptive only
- Height (cm) and weight (kg) as BMI, descriptive only
- Physical health diagnoses, descriptive only
- Parental 'about yourself' questionnaire, descriptive only

Scales of suicidal ideation, hospitalizations, mood symptoms, behavioural and functional difficulties, quality of life ratings

- Ask Suicide-screening Questions (ASQ) for suicidal ideation and behaviour, binary
- Child Behaviour Checklist (CBCL), continuous
- Youth Self-Report (YSR) for behavioural and emotional problems, continuous
- KIDSCREEN-52 for quality of life, all 10 domains continuous
- Difficulties in Emotion Regulation Scale – 18 (DERS-18), for young people, DERS-29 for parents, continuous
- Hospitalisations of participants, binary
- Social transition questionnaire, descriptive only

Experiences of therapeutic options

- Rates of referral to, uptake of and completion of:
- Psychological therapy, binary
- Occupational therapy, binary
- Speech and language therapy, binary
- Clinical nursing, binary
- Youth work support, binary
- School/College support, binary
- Non-endocrine pharmacological treatments, binary

8.3 SAMPLE SIZE JUSTIFICATION

The anticipated sample size is approximately 3600 participants (CYP- parent/caregiver dyads). This sample size is based on the expected clinic prevalence of gender related distress (assuming 80% recruitment of those presenting at the CYPGS), allowing for sufficient power to detect meaningful differences and associations in the primary and secondary outcomes.

This sample size will allow for meaningful effect sizes to be determined within subgroups of this larger population. As an example, it is estimated that those diagnosed with neurodevelopmental traits or disorders will make up around 15% (540) participants in the Horizon cohort. With around a 50/50 split of birth registered males and females within this subgroup, sample size simulations estimate that it would be possible to determine a standardised effect size of approximately 0.32,

with an estimated 90% power between birth registered sexes within the Neurodivergent population.

8.4 STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES

Descriptive statistics will be presented for all outcomes, in the form of means and standard deviations for continuous outcomes, and count and proportion for binary or categorical outcomes. Tests will be carried out between the outcomes and the demographics to determine associations. Differences between the participant and parent reported outcomes, where both are available, will also be investigated. This will be done using paired t-tests or Wilcoxon signed-rank tests. Intraclass Correlation Coefficients will be calculated to assess agreement between the participant and parent reports.

Further information on analysis methods can be found in the Statistical Analysis Plan for PATHWAYS Horizon.

8.4.1 STATISTICAL METHODS FOR PRIMARY OUTCOME

The primary outcome will be analysed using a linear mixed model. This will account for the repeated measured design, and using maximum likelihood estimation allows for handling of missing follow-up data.
The fixed effects in the model will be timepoint, gender incongruence, age, site, neurodevelopmental conditions. The random effects in the model will be participant, to allow for random intercepts.
Estimates presented from this model will be point estimates and the 95% confidence intervals of those estimates.

8.4.2 STATISTICAL METHODS FOR SECONDARY OUTCOMES

8.4.2.1 CONTINUOUS OUTCOMES

For continuous outcomes, the same analysis method will be used as are in the primary analysis. The fixed and random effects will also be the same as used in the primary analysis.

8.4.2.2 BINARY OUTCOMES

For binary outcomes, a similar method as used in the primary outcome analysis will be used. A mixed-effects logistic regression will be used in place of the mixed linear model.
The fixed effects and random effects will be the same as those used in the primary analysis.

8.4.2.3 TIME-TO-EVENT OUTCOMES

For time to event outcomes, a cox proportional hazards model will be used. Other models will be considered if the proportional hazards assumption does not hold.

8.5 INTERIM ANALYSES (STATISTICAL)

There is no planned interim analysis.

8.6 METHODS FOR ADDITIONAL ANALYSES (E.G. SUBGROUP ANALYSES)

The below CYP subgroups are planned to be used as subgroup analyses.

- Birth-registered sex
- Age at referral
- Neurodevelopmental and mental health diagnoses
- Social transition status
- Adverse life experiences

These analyses will be carried out using interaction terms in mixed models, and stratified analyses to compare separate analyses within each subgroup. Further subgroup analyses and analysis specifications will be detailed in the statistical analysis plan.

8.7 ANALYSIS OF NOVEL OUTCOME MEASURE

The primary aim is to establish the psychometric properties of the novel measure. The most important characteristics are inter-rater and test-retest reliability, but we also want to understand its convergent validity with the primary outcome measure, KIDSCREEN-10 and other outcome measures of mental health and behaviour, gender identity and body dysphoria. All of these established measures generate continuous scores.

Individual items in the novel measure will a priori map to measure domains, e.g., gender identity, emotions, family life, etc. Each domain will generate an individual score which will form a component of the total score. Domain will be ordinally or continuously distributed, and the total score will be continuous.

Inter-rater and test-retest reliability using intre-clss correlations (ICCs) will focus on the total score; while these characteristics of domain scores will be extracted, it is recognised that there will be lower levels of agreement. Similarly, associations to other outcome measures will be evaluated with ICCs, with a priori expectations of relative convergence amongst measures tapping overlapping concepts and experiences.

The measure will be considered a valid primary outcome for gender incongruence if inter-rate and test-retest reliability are both 0.7.

8.8 METHODS TO HANDLE MISSING DATA

Missing data will be dealt with using the analysis method chosen. Using a linear mixed model with maximum likelihood estimation deals with missing data under the Missing at Random method. To determine if the data is not Missing at Random, we will conduct a sensitivity analysis for Missing Not at Random (MNAR).

Multiple imputation will be considered as a method to deal with missing data in relation to the level of missingness in the outcome. Participants will only have outcomes imputed for timepoints that they could have attended, in relation to the year they were consented into the study. For example, a participant consented with only 3 years of follow-up possible will not have a 4- or 5-year follow-up outcome imputed.

8.9 POPULATIONS UNDER INVESTIGATION

The population under investigation are children and young people referred to national gender services for young people in the UK.

8.10 METHODS TO HANDLE COMPLIANCE

As this is an observational study, there is no intervention or control. Therefore, there is no therapy or intervention to comply with.

8.11 *SENSITIVITY ANALYSIS*

There are no planned sensitivity analyses for the Horizon study.

8.12 PLANS TO GIVE ACCESS TO THE FULL PROTOCOL AND PARTICIPANT LEVEL-DATA

The protocol will be published in an open-access journal, including an easy read version for lay participants. The deidentified dataset (in which individuals cannot be identified) may be available upon request following the development of an access plan drawn up in consultation with the PPI Advisory Boards and the Oversight Committees. Data will not be available to researchers outside the PATHWAYS group during the time the study is ongoing, except for the purposes of audit and regulatory inspections.

9. OVERSIGHT AND MONITORING

9.1 PATHWAYS 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.

9.2 PROGRAMME STEERING COMMITTEE (PSC)

The PSC will be composed of a majority of independent members. The PSC is an executive committee, reporting to the funder (National Research Collaboration Programme), and the sponsor. The PSC is formally appointed by the National Institute for Health and Care Research (NIHR) and members will receive individual letters from NIHR confirming their role. Independent members will be independent of the Sponsor organisations and of any recruiting study sites.

The study may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority based on reasons presented by the Data Monitoring Committee, PSC, Regulatory Authority or REC concerned. If the study 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 study.

9.3 DATA MONITORING COMMITTEE (DMC)

The DMC will be composed of a minimum of three independent members: a statistician and a minimum of two clinicians. The DMC is an advisory committee, reporting to the Programme Steering Committee. The DMC is formally appointed by NIHR and members will receive individual letters from 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 [35]. Selected data from PATHWAYS HORIZON will be presented to the DMC to provide important context for interpreting data from the PATHWAYS Trial.

9.4 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.

10. MISCELLANEOUS

10.1 PLANS FOR INDEPENDENT AUDIT

There are no current plans for an independent audit to be conducted.

10.2 PUBLICATION POLICY

All proposed publications will be described in a brief abstract that includes headings of: Background, Methods, Proposed Results, Likely implications. They will be reviewed by the PMG who may make suggestions and will approve them. The abstract should also include the proposed authorship list. PATHWAYS aims to be inclusive in authorship and will follow the recent KCL guidance on considering credit in a number of areas including: conceptualisation, data collection, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, visualisation and writing (both original and reviewing/editing). Through PATHWAYS Engagement Advisory Groups, we will seek the views of the community on the topics and breadth of publications. Whenever appropriate, members of the Advisory Groups will be offered authorship on publications.

All publications will be shared with the funder prior to submission for awareness. They will also be shared with the Programme Steering Committee and Data Monitoring and Ethics Committee. All publications will be made open access, whether through green or gold routes.

10.3 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.

10.4 END OF STUDY

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

10.5 CONFIDENTIALITY

When consent forms are signed electronically, a copy will be provided to the participant, a copy will be filed in the medical records, and a copy will be filed in the Investigator Site File. Participant's initials, date of birth and ethnicity will be entered into the study database, but no more identifying information will be collected outside the recruiting study site. Personal and contact information will be transcribed into a KCL data safe-haven by delegated Research Associates (see section 5.2). Within site, an Investigator Site File will be maintained by the site PI. 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).

10.6 FUNDING

This project (NIHR167530) is funded by the National Research Collaboration Programme, 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.

10.7 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 from HORIZON.

10.8 INSURANCE AND INDEMNITY

The lead sponsor, KCL, will take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting. KCL also provides cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions).

The co-sponsor, South London and Maudsley NHS Foundation Trust, take responsibility for arranging the initiation and management of this research, and will take responsibility for ensuring that appropriate standards, conduct and reporting are adhered to regarding its facilities and staff involved with the project.

UK NHS recruiting sites provide indemnity in the event of clinical negligence.

10.9 ARCHIVING

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will distribute as appropriate for the purpose of archiving. The CIs will appoint named individuals within the research team to be responsible for archiving the documents which are, or have been, contained in the TMF and, access to those documents shall be restricted to those appointed individuals.

At the end of the study, all data will be stored and archived in line with Sponsor requirements for a period of 25 years as defined in the Organisation Information Document provided for site set up. Recruiting sites will be responsible for archiving the source data and Investigator Site Files as per Trust/local policies.

10.10 INTELLECTUAL PROPERTY (IP)

The expected IP developed during the study will be the new novel outcome measure developed in this study (see section 4.8). Copyright and IP will be held by KCL.

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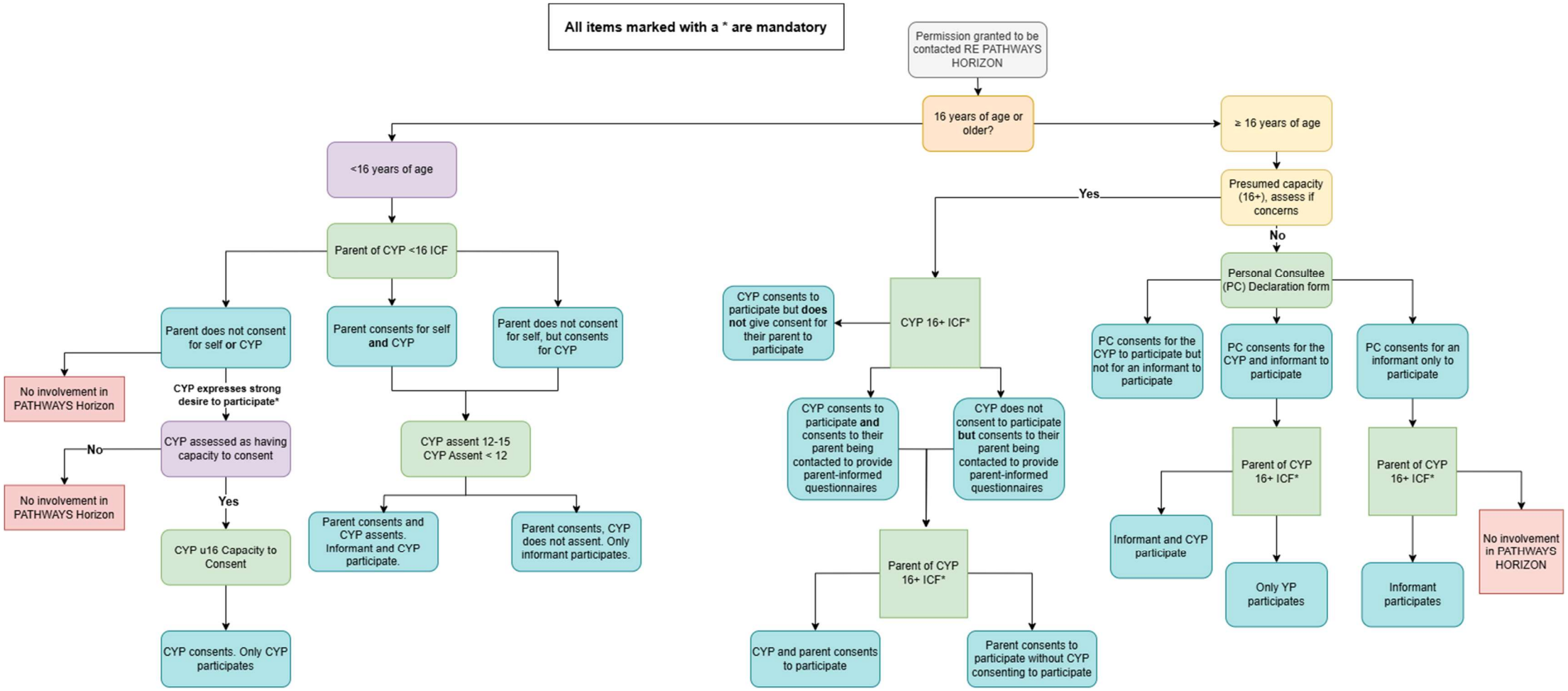
Annex 1 – Consent Flowchart



Annex 2 – Individual Schedule of Events

Table 2: Schedule of Events for information collected from CYP

Event/Form	Domain, information source (see legend)	Baseline	Month 12	Month 24	Annual Follow Up	Estimated completion time (minutes)
Informed consent/ assent	SQ (1)	X				10
Quality of Life (KIDSCREEN-52)	SQ, PQ (2)	X	X	X	X	7
Annual health update (CYP 16+ only)	SQ, PQ (6) (7)		X	X	X	6
Gender Identity Questionnaire	SQ, (3)	X	X	X	X	1
Social Transition Questionnaire	SQ (3)	X	X	X	X	1
Anxiety and depression symptoms (RCADS-25)	SQ, PQ (4) (7)	X	X	X	X	5
Suicide/ Self Harm (ASQ)	SQ, PQ (4) (7)	X	X	X	X	1
Gender dysphoria (UGDS-GS)	SQ (3) (7)	X	X	X	X	3
Body image/ dysphoria (BIS-GS)	SQ (3)	X	X	X	X	3
Emotional Dysregulation (DERS-18)	SQ, PQ (4)	X	X	X	X	3
Sexual Attraction Questionnaire (CYP 12+ only)	SQ (3)	X	X	X	X	1
Romantic Relations (ALSPAC measure; CYP 12+ only)	SQ (3)	X	X	X	X	5
Parental support (PAGES-Y)	SQ (4)	X	X	X	X	3
Trauma (APCTSS)	SQ, PQ (4)	X	X	X	X	2
Emotional & Behavioural Problems (CBCL, YSR)	SQ, PQ (4)	X	X	X	X	15
Eating Problems (SCOFF)	SQ, PQ (4)	X	X	X	X	1
LEGEND **Domains:** 1=protocol adherence; 2= personal priorities and quality of life; 3= gender; 4=mental health; 5= neurodevelopmental difference; 6=physical health; 7=adverse events **Information source:** R=researcher-completed; SQ=self-reported questionnaire; PQ=parent-reported questionnaire; D=direct observation/examination						

* *If a participant turns 16 during the study, consent must be sought*

Table 3: Schedule of Events for information collected from parents/carers/legal guardians

Event/Form	Domain, information source (see legend)	Baseline	Month 12	Month 24	Annual Follow Up	Estimated completion time (minutes)
Informed consent/ assent	PQ (1)	X				10
ADHD (SNAP-IV)	PQ (5)	X				3
Autism (SCQ)	PQ (5)	X				5
Parental 'About yourself' Questionnaire	PQ(3)	X				1
Gender Identity Questionnaire	SQ, PQ**	X				
Quality of Life (KIDSCREEN-52)	SQ, PQ (2)	X	X	X	X	7
Annual health update (Parents of CYP under 16 only)	SQ, PQ (6) (7)		X	X	X	6
Anxiety and depression symptoms (RCADS-25)	SQ, PQ (4) (7)	X	X	X	X	5
Suicide/ Self Harm (ASQ)	SQ, PQ (4) (7)	X	X	X	X	1
Emotional Dysregulation (DERS-P)	SQ, PQ (4)	X	X	X	X	3
Parental Support (PAGES-P)	SQ, PQ (4)	X	X	X	X	3
Trauma (APCTSS)	SQ, PQ (4)	X	X	X	X	2
Emotional & Behavioural Problems (CBCL, YSR)	SQ, PQ (4) (7)	X	X	X	X	15
Eating Problems (SCOFF)	SQ, PQ (4)	X	X	X	X	1

LEGEND
Domains:
1=protocol adherence; 2= personal priorities and quality of life; 3= gender; 4=mental health; 5= neurodevelopmental difference; 6=physical health; 7=adverse events
Information source:
R=researcher-completed; SQ=self-reported questionnaire; PQ=parent-reported questionnaire; PQ**= parent reported questionnaire at baseline only; D=direct observation/examination

* *If a participant turns 16 during the study, consent must be sought*

Table 4: Schedule of Events for information collected by clinicians/researchers

Event/Form	Domain, information source (see legend)	Baseline	Month 12	Month 24	Annual Follow Up	Ongoing*	Estimated completion time (minutes)
Registration form & consent	R (1)	**X**					**5**
Eligibility	R (1)	**X**					**10**
Medical history	D (6)	**X**					**150**
Demographic data	D (1)	**X**					**2**
Status form	R (1)		**X**	**X**	**X**		**1**
Withdrawal form	R (1)					**X**	**2**

LEGEND
Domains:
1=protocol adherence; 2= personal priorities and quality of life; 3= gender; 4=mental health; 5= neurodevelopmental difference; 6=physical health; 7=adverse events
Information source:
R=researcher-completed; SQ=self-reported questionnaire; PQ=parent-reported questionnaire; D=direct observation/examination;

* *If a participant turns 16 during the study, consent must be sought*

Table 5: Schedule of Events for novel outcome measure

Event/Form	**Domain, information source (see legend)**	**Baseline**	Follow-up (within 1-month of baseline)	**Follow-up (within 6-months of baseline)**	**Estimated completion time** (minutes)
Informed consent/ assent	SQ, PQ	**X**			10
Interview	D (2) (3) (4) (6)	**X**	**X**	**X**	60
Personal treatment priorities	SQ, PQ (2)	**X**			5
Quality of Life (KIDSCREEN-52)	SQ, PQ (2)	**X**			7
Anxiety and depression symptoms (RCADS-25)	SQ, PQ (4) (7)	**X**			**5**
Gender dysphoria (UGDS-GS)	SQ (3)	**X**			**3**
Body image/ dysphoria (BIS-GS)	SQ (3)	**X**			**3**
Emotional & Behavioural Problems (CBCL, YSR)	SQ, PQ (4)	**X**			**15**

Legend

Domains:

1=protocol adherence; 2= personal priorities and quality of life; 3= gender; 4=mental health; 5= neurodevelopmental difference; 6=physical health; 7=adverse events

Information source:

R=researcher-completed; SQ=self-reported questionnaire; PQ=parent-reported questionnaire; D=direct observation/examination