HRA PROTOCOL COMPLIANCE DECLARATION:

This protocol has regard for the HRA guidance and order of content

FULL/LONG TITLE OF THE STUDY

Outcomes and Predictors of Outcome for Children and Young People Referred to UK Gender Identity Development Services: A Longitudinal Investigation

SHORT STUDY TITLE / ACRONYM

LOGIC: Longitudinal Outcomes of Gender Identity in Children
LOGIC-Q: Longitudinal Outcomes of Gender Identity in Children - Qualitative Study

PROTOCOL VERSION NUMBER AND DATE

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LIST of CONTENTS

HRA PROTOCOL COMPLIANCE DECLARATION: i
TITLE PAGE i
RESEARCH REFERENCE NUMBERS i
LIST of CONTENTS ii
LIST OF ABBREVIATIONS iv
STUDY SUMMARY v
FUNDING AND SUPPORT IN KIND v
ROLE OF STUDY SPONSOR vi
ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS/FUNDER vi
STUDY PROTOCOL 1
1 BACKGROUND 1
2 RATIONALE 2
3 RESEARCH QUESTION/AIM(S) 2
3.1 Objectives 3
3.2 Outcome 3
4 THEORETICAL FRAMEWORK FOR THE QUALITATIVE STUDY 4
5 STUDY DESIGN 5
6 METHODS of DATA COLLECTION 5
7. METHODS of DATA ANALYSIS 7
8 STUDY SETTING 10
9 SAMPLE AND RECRUITMENT 10
9.1 Eligibility Criteria 10
9.1.1 Inclusion criteria 10
9.1.2 Exclusion criteria 11
9.2 Sampling 11
9.2.1 Size of sample 11
9.2.2 Sampling technique 12
9.3 Recruitment 12
9.3.1 Sample identification 12
9.3.2 Consent 13
10 ETHICAL AND REGULATORY CONSIDERATIONS 15
10.1 Assessment and management of risk 15
10.2 Research Ethics Committee (REC) and other Regulatory review & reports 16
10.3 Peer review 17
10.4 Patient & Public Involvement 17

10.5 Protocol compliance 18
10.6 Data protection and patient confidentiality 19
10.7 Indemnity 20
10.8 Access to the final study dataset 20
11 DISSEMINIATION POLICY 21
11.1 Dissemination policy 21
11.2 Authorship eligibility guidelines and any intended use of professional writers 21
12 REFERENCES 20
13. APPENDICES 22

LIST OF ABBREVIATIONS

Term	Definition
AIC	Akaike Information Criteria
ASD	Autistic Spectrum Disorder
BAME	Black, Asian, and Minority Ethnic
CBCL	Child Behaviour Checklist
CHU-9D	Child Health Utility 9 Dimensions
CI	Chief Investigator
CRF	Case Report Form
CYP	Children and Young People
GCP	Good Clinical Practice
GD	Gender Dysphoria
GI	Gender Identity
GIDS	Gender Identity Development Service
GDPR	General Data Protection Regulation
GnRH	Gonadotropin Releasing Hormone
GLM	General Linear Model
HRA	Health Research Authority
HS&DR	Health Service and Delivery Research
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
NMB	Net Monetary Benefit
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient Public Involvement
QALY	Quality Adjusted Life Years
REC	Research Ethics Committee
SDQ	Strengths and Difficulties Questionnaire
SDV	Source Document Verification
SRS-2	Social Responsiveness Scale
SOP	Standard Operating Procedure
SSC	Study Steering Committee
YSR	Youth Self Report

STUDY SUMMARY

Study Title	Longitudinal Outcomes of Gender Identity in Children
Internal ref. no. (or short title)	LOGIC
Research Questions/Aims	1. What is the profile of children and young people (CYP) referred to GID services? 2. What proportion of children and young people, aged 3-13 years when their referral was accepted to these services experience ongoing gender dysphoria; and go on to have physical treatment? What are the predictors of such occurrences? 3. What is the impact of a) physical treatment, b) social transition, and c) co-occurring autism on physical health, psychological wellbeing, quality of life, peer and family relationships, and cost to the NHS and other public services? 4. What is the experience of children and young people, and their families over time referred to GID services?
Study Participants	Children and young people (CYP) aged 3- 13 years at the time of referral acceptance to the UK Gender Identity Development Service (GIDS), and their caregivers.
Planned Size of Sample (if applicable)	We will aim to recruit a total of 638 children and young people to the quantitative study. A total of 40 families, consisting of both the children and young people attending the UK GID service and their caregivers, will be recruited to the qualitative arm of the study.
Follow up duration (if applicable)	2 years
Planned Study Period	48 months

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**

NIHR Health Services & Delivery Research Programme	£ 1.3 million financial support (for overall study)

ROLE OF STUDY SPONSOR

The sponsor is responsible for confirming that the study design has integrity, the resources required for initiation are secured, all applicable regulatory approvals have been received before commencement, and that arrangements are in place for monitoring and reporting to ensure research conduct is in compliance with Good Clinical Practice (GCP) and all applicable laws and regulations. The sponsor will also confirm that there is a clear dissemination and data retention plan once the study has closed.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS/FUNDER

Study Steering Group/Funder

The Study Steering Committee (SSC) will provide overall supervision for the project on behalf of the Project Sponsor and Funder to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. It will include an independent chair, PPI representatives, and independent clinicians and academics who will meet every 4-6 months. These will report to NIHR and the sponsor as required. There will also be ongoing communication every 6-8 months with 'internal' PPI advisory groups consisting of children and young people attending the GID service and their parents.

KEY WORDS: Gender dysphoria; Gender identity; Children and Young People; Prospective cohort; Longitudinal

STUDY PROTOCOL

Longitudinal Outcomes of Gender Identity in Children (LOGIC)

1 BACKGROUND

Emerging data from several countries suggest that gender diversity in children and young people is more common than previously thought (1). This is reflected in the significant increase in referrals reported in gender clinics across a number of countries. For instance, in the UK, rates of referral rose from 97 to 2,519 yearly referrals in approximately a decade. Such rise in referrals is also accompanied with a younger age at time of referral and a rise in children accessing physical treatments (2-4).

While not all gender-diverse children and young people will experience gender dysphoria (that is, the experience of distress associated with a mismatch between the sex assigned at birth and gender identity), a proportion do. The available evidence suggests that gender dysphoria is associated with a range of negative mental and physical health difficulties, including depression, anxiety, suicidality and substance abuse (5-10). Current NHS intervention for children and young people experiencing gender dysphoria is aimed at alleviating dysphoric feelings, improving psychological wellbeing and supporting young people and their families to make informed decisions about treatment and the meaning of gender identity within their lives and contexts (11). However, the evidence base on which the current treatment protocols are based is widely acknowledged to be both limited and shifting (12). To date, no information exists to help us clinically predict individual gender and psychosexual developmental pathways (12). It is difficult to estimate what proportion of younger pre and peri-pubertal children and young people referred to NHS services will later access physical treatment to suppress puberty. We are also currently unaware of the factors that predict the likelihood of receiving such treatment from the NHS, and the physical and psychological impact of such treatment (13).

Internationally, the need for longitudinal evidence to inform the care of gender diverse children and young people is well established in the literature (12). In light of this dearth of research, the proposed study aims to investigate the mental and physical health outcomes of children and young people referred to the UK's Gender Identity Development Service. It will compare the outcomes of those who pursue physical intervention to those who do not, and explore the impact of factors such as co-occurring Autism Spectrum Disorder (ASD) and a decision to socially transition (i.e. change name, pronouns, clothing etc. to better reflect their gender identity), on such outcomes over time.

Furthermore, it will describe the experiences of those referred onto the service and their families, in order for us to better understand their changing perceptions of gender identity within the context of their lives, the factors that may influence such changes, and how their experiences of help seeking, health services and therapies can be improved.

2 RATIONALE

Very little is known overall about the profile of children and younger adolescents referred to Gender Identity Development (GID) services. At present, we are unaware, both in the UK and internationally, of the outcomes and likely trajectories of children and young people presenting to these services.

A key question for the NHS pertains to the proportion of gender diverse children and young people presenting to services who later go on to receive treatment with hormone blockers, and which factors predict this. Additionally, major knowledge gaps currently exist in relation to the immediate and long-term impact of a) physical treatment commencing in early puberty b) early social transition c) and co-occurring Autistic Spectrum Disorder (ASD).

This study will characterise the entire cohort of children and younger adolescents aged between 3 and 13 years at the time of referral to a GID service. It will help us develop a greater understanding of the individual differences in those referred to the service. The findings generated from this research will enable services to provide better, more individualised care, which will provide immediate benefits to patients and their families.

3 RESEARCH QUESTION/AIM(S)

1. What is the profile of children and young people referred to GID services?
2. What proportion of children and young people, aged 3-13 years when their referral was accepted to these services experience ongoing gender dysphoria, and go on to have physical treatment? What are the predictors of such occurrences?
3. What is the impact of a) physical treatment b) social transition c) co-occurring autism on, physical health, psychological wellbeing, quality of life, peer and family relationships and cost to the NHS and other public services?
4. What is the experience of children and young people, and their families after they are referred to GID services?

3.1 Objectives

Our objective is to undertake a prospective longitudinal study of children and young people aged 3-13 years at the time of referral acceptance to the UK's GID service, consisting of both:

1. quantitative assessments at baseline and at yearly follow-up over two years;
2. qualitative interviews with both those referred and their caregivers, at baseline and at yearly follow-up over two years in a sub-sample of 40

3.2 Outcome

This research will generate important new insights about a population of children and young people who experience significant distress about their gender identity and are referred to a GID service for support and/or long-term intervention. Making as accurate an assessment as possible at a younger age has profound implications for the psychological and physical wellbeing of the individual but also for the cost to the NHS and public funds. The study will seek to identify the factors that influence this group's mental health, behavioural and emotional functioning, and quality of life. It will identify the factors that influence whether a child or young person chooses physical/endocrine treatment and compare the mental health, wellbeing and physical health outcomes for those in receipt of endocrine treatment with those of a similar age/pubertal stage not receiving such treatment. It will also explore the impact of factors such as a) co-occurring ASD, and b) a decision to socially transition, on outcomes over time.

Health economic data will be generated regarding the costs and consequences of a range of service, intervention and children and young people/family characteristics. The qualitative component of the longitudinal study will complement the quantitative elements by providing in-depth data on experience of gender diversity issues and services and how these change over time from the perspective of children and young people and their families. This will include those who do not progress through GIDs services as well as those who do.

The data generated will be used as material to develop multi-media resources to inform children and young people and their families about the differing narratives and trajectories of this group. These resources will be developed in consultation with key stakeholders and will aim to convey, in a child and family centred way, the 'human stories behind the figures'. These multi-media resources will also assist in the education of NHS commissioners and clinicians, schools and other relevant service providers, and thereby help to enhance therapies and support for children and young people and their families.

LOGIC's key findings will be disseminated through diverse and innovative methods that target policy makers, service planners, accreditation bodies, clinicians and service users in order to achieve adoption of our recommendations. A project website will be established to facilitate communication of findings and dialogue with key stakeholders. The research will be published in high impact, open access, Journals (e.g. the Lancet, Lancet Child and Adolescent Health, BMJ). Findings will be presented at national and international conferences in the field of Gender Identity Development (e.g. WPATH, EPATH, BAGIS) and Child and Adolescent Health (e.g. ACAMH, RCPH, British Association of Community Child Health, European Society for Paediatric Endocrinology, World International Meeting of Pediatric Endocrinology).

Relevant findings will be communicated and discussed with key external stakeholders including NHS service commissioners, Adult Gender Identity Health Services, CAMHS, primary care, schools and education departments. NHS treatment protocols and guidance will be informed and updated with the findings from this research so that the NHS, service commissioners and clinicians will be better informed with regard to improving both service delivery and individualised care for children and young people and their families.

4 THEORETICAL FRAMEWORK FOR THE QUALITATIVE STUDY

There is a paucity of previous research in this area to guide the selection of a specific theory of childhood gender identity variance to inform the qualitative analysis. Moreover, in keeping with our inductive approach, it is important that the products of the analysis arise from the data and are not imposed on it, and so selecting a specific theory would be premature at this stage. Nevertheless, we are aware of the importance of theory in qualitative analysis, and over the course of the qualitative study we will identify and explore theory that could illuminate the analysis (14).

The method of analysis will be pluralistic. This avoids the pitfalls of constraining the analyses to a specific 'brand' or framework of qualitative analysis and reflects recent recommendations for qualitative researchers to innovate and adjust their methods as appropriate to their data and research goals to achieve 'fidelity' to the data and 'utility' for the particular research questions (15, 16). Others have argued that combining two or more analytical frameworks can produce richer understandings that better reflect the complexity of human experience than drawing on a single framework (17).

5 STUDY DESIGN

This is a prospective cohort study employing a mixed-methods design. It will include children and young people aged 3-13 years at the time their referral was accepted by the UK'S GID service, and their families. It will consist of both quantitative assessments and qualitative interviews at baseline and two further yearly follow-up time points. Please see the attached Gantt chart (Appendix 2) for a detailed timeline of the study.

6 METHODS of DATA COLLECTION

a) Quantitative study

Assessments will be facilitated by two Research Assistants (with supervision and assistance from a Research Coordinator) based at the Tavistock Clinic in London. Assessments will be carried out and recorded online using 'Red Pill', a GDPR-compliant, encrypted online database co-constructed with UCL's PRIMENT Clinical Trials Unit. Participants undertaking online assessments will be assisted either by telephone or via videocall using 'Telemedicine', a secure technology platform similar to 'Zoom' or 'Skype' that allows the researchers to assist, speak to and see participants, dependent on families' preferences and access to technology. In a minority of cases, in case of technical difficulties or participants' preference, we may carry out assessments on site or at a place of the participant's choosing. As the quantitative arm of the study aims to collect data from 638 participants at three timepoints, it will not be possible to collect data from all participants in person within the study's timeframe. For this reason, we are opting to give participants a choice in how to be complete the assessments.

Assessments will include measures of: gender dysphoria and gender identity; social transition status; mental health and psychological wellbeing; Autism Spectrum Disorder traits; self-evaluation of puberty stage, height and weight; cognitive development; quality of life; peer and family relationships; socio-cultural and demographic factors; and health care and societal costs. For a sub-set of participants who will be referred and seen at endocrine clinics, we will request access to data that is routinely collected form those clinical services. As per current NHS treatment protocols, those receiving physical treatment with hormone blockers (GnRH agonists) and/or cross-sex hormones, will be monitored for changes in blood count, renal and liver function, skeletal maturity and bone density and Tanner pubertal staging. Capturing this data will allow adult height predictions to be tracked, and

clinical measurements of body proportions, height, spinal height, shoulder and hip widths and body composition by bioelectrical impedance.

Please see Appendix 3 for a table of all proposed measures.

b) Qualitative study

The qualitative study will involve semi-structured, topic-guided interviews with a purposively sampled sub-set of children and young people from the quantitative study and their parents. We anticipate that the qualitative research associate employed on the LOGIC study will conduct most of the interviews, although where logistical issues arise, other suitably experienced researchers employed on the study may also conduct some interviews. All researchers involved in conducting the qualitative interviews will receive specific training and feedback for this project (see further details of training below) to ensure interviews are developmentally appropriate, conversational in approach and responsive to participants' needs. Interviews will follow the structure of the topic guides attached (Appendix 4), which were developed in collaboration with the peer researcher, wider project team, and the GID service and will be further refined in consultation with external PPI groups. Following good practice in qualitative research, the topic guides will also be developed over the course of the study to explore unanticipated and emerging issues (including over the three interview time points) as informed by ongoing analysis.

To maintain continuity for participants we will arrange for the same interviewer to conduct all three successive interviews with each participant, where possible. We anticipate that most participants will be interviewed face-to-face in their homes or other private place of their choosing, although where participants prefer to be interviewed via another suitable medium (such as the telephone, or via videocall) we will try to accommodate their preferences. We will aim to speak with children and young people and parents separately at least for part of the interviews, nevertheless we will accommodate the preferences of those who prefer wholly joint interviews as necessary. Interviews will be audio-recorded using digital recorders with encryption facilities, and transcribed by a professional transcription agency. The transcription agency will be asked to sign the Trust's Data Processing Agreement stating that they will be processing the data solely for the purpose of transcription, and that they will be responsible for any data breaches arising whilst the data is in their care. All transcripts will be uploaded and downloaded by the transcription agency via a military grade 128-bit Transport Layer Security (TLS) encryption for security. Transcripts will be pseudo anonymised by the research assistants/coordinator and checked for accuracy before analysis.

Given the sensitivities involved in eliciting children and young people and families' experiences of gender diversity we will ensure interviewers have excellent interpersonal abilities and experience relevant to conducting qualitative interviews in sensitive settings. Specialist training in interviewing children and young people and their parents will be provided, including rapport building, question technique and responding to create a sense of safety and comfort according to the needs of individual participants. We will draw upon the specific expertise of the GIDS PPI group, peer researcher, external user (stakeholder) advisory group and clinical team members to ensure the interviewers are sensitive to the particular needs of gender diverse children and young people and their families. Interview quality will be supported by key study team members (particularly BY, EK and TW) listening to interview audio-recordings and meeting regularly with interviewers to review transcripts.

We will use a range of resources and strategies to support children and young people interviews, including activities, games, digital technology, creative arts/drawing and toys according to interviewee preference and developmental needs (18). For example, we will use computer assisted interview techniques where these might help to facilitate the engagement of young children, the situationally shy and those with ASD (19, 20). Similarly, we will draw on children and young people's special interests such as video gaming or digital media characters to provide openers for exploring their thoughts about gender, particularly for young people with ASD. Discussions with families at the time of arranging the interviews and before commencing interviews will be used to gauge the needs, preferences and interests of children and young people so we can prepare for and adapt interviews accordingly. This will also include establishing preferred names, pronouns and the particular phrases that children and young people use when referring to gender identity issues, including any changes in these preferences over the course of each participant's three successive interviews.

7. METHODS of DATA ANALYSIS

a) Quantitative study

Statistical analysis will be undertaken by the PRIMENT CTU team who will download the data directly from the Red Pill online database and analyse it using STATA. The characteristics of the children and parents and the outcomes will be presented using mean (SD), median (IQ range) or frequencies (proportion) as appropriate. A logistic regression model will be used to examine the

association between the pre-specified explanatory variables and persistent or ongoing GD. Appropriate regression models will be used to investigate the explanatory variables for the secondary outcomes, physical/endocrine intervention, Mental Health (SDQ), Behavioural and Emotional Functioning (CBCL, YSR) and Quality of Life (Kidscreen 52, CHU-9D). Models will account for the repeated measures of Mental Health and Behavioural and Emotional functioning and quality of life outcomes and the relevant explanatory variables. Exploratory subgroup analyses will be carried out for the pre-pubertal children and children with autistic traits (as assessed using the AQ) using descriptive statistics and appropriate regression models, where possible. Physical and psychological health outcomes over time will be compared descriptively between those in receipt of hormone blockers (GnRH agonists) and those of a similar age/pubertal stage who progress through puberty without such intervention.

We will report descriptive statistics for health care resource use for children in active contact with GID versus those who are not by a) physical treatment b) social transition c) co-occurring ASD. Published sources will be used to calculate mean total costs for the three groups. Costs will also be reported alongside Quality of Life (Kidscreen 52, CHU-9D), Mental Health (SDQ), and Behavioural and Emotional functioning (CBCL, YSR) as it is not clear what relationship increased costs may have with outcomes for active contact with GID versus not. In particular increased costs related to additional mental health service use will have different implications to increased costs as a result of physical treatment. We will investigate key predictors of costs by including pre specified explanatory variables including "active contact with GID" in appropriate general linear models (GLM). The most appropriate GLM will be chosen using the Akaike information criteria (AIC). This will allow for an estimate of the additional cost or cost-savings associated with active GID contact. Similar models will also be run to test if active contact with GID is related to improvements in Quality of Life. This will be based on quality adjusted life years (QALYs) calculated using the CHU9D, the relevant tariff and the area under the curve. We will run an additional series of GLMs to calculate the net monetary benefit (NMB) of contact with GID services, where for each patient QALYs will be multiplied by a range of values of willingness to pay for a QALY minus the total cost of health and social care services.

Bias due to any missing data in the database and in the cohort study will be investigated. The regression models will be adjusted for predictors of missingness if required and multiple imputation may be used to impute the missing explanatory variables if appropriate. A detailed statistical analysis plan will be prepared nearer the analysis stage.

Should individuals drop out, we will describe and compare the characteristics and outcomes of those who drop-out from the cohort study to those who remain in the study (e.g. demographic characteristics, previous responses, who they are assessed by) to understand whether these have influenced their motivation to leave the study.

All assessment data will be inputted electronically onto the *Red Pill* database system directly. This is a GDPR-compliant, encrypted online database co-constructed with UCL's PRIMENT team. For further information, please see section 10.6.

b) Qualitative study

Analysis of interview transcripts will be inductive, with the key aim of informing health services for children and young people and their families, whilst providing wider contextual insights to understand why, how and for whom service development is needed. Initial analytical questions to be addressed include:

- how gender identity and dysphoria is experienced by participants and how this experience changes over time;
- how a) social transition b) psychological and physical treatment c) a co-occurring diagnosis of ASD is experienced;
- the extent to which assessment processes and physical intervention may reinforce societal 'gender binary stereotypes' or be inadvertently iatrogenic;
- how participants engage with dilemmas about capacity to provide informed consent to treatment particularly in the context of mental health problems, ASD or varying cognitive and emotional maturity;
- how services and therapeutic protocols can better respond to the needs of children and young people and families;
- what service and treatment outcomes are important to children and young people and their families.

Analysis will be interpretive and pluralistic, drawing on both narrative and thematic approaches (17, 21) and seeking to identify and explore theory that could illuminate interpretations of the data. Both thematic and narrative analytical frameworks have been successfully combined previously (22), including in a previous longitudinal qualitative study of the daily lives, networks and life transitions of children and caregivers (23). Thematic analysis is flexible and accessible and so particularly suited

to our participatory co-production approach and to our aims to inform practice and policy (17). Narrative analysis, which focuses on how participants order, sequence and present their stories and 'turning points' (24) is well suited to the qualitative study's central focus on experiences of changes in gender identity over time and how this links with well-being and experiences of services.

Children and young people and parent data will initially be analysed separately to ensure their perspectives are given equal 'weight' before within family comparisons to identify commonalties and divergences between children and young people and parents. We will treat divergences, not necessarily as contradictions and be open to these as opportunities for conceptual development (25).

As year 2 and 3 data become available we will examine continuities and changes over time, exploring and 'testing' explanations of such patterns (26), and drawing on data from the quantitative cohort to illuminate the analysis (27). The qualitative study research associate and BY will lead the analysis, whilst also meeting regularly with the peer researcher (TW) and wider team to facilitate investigator triangulation. Reports/presentations on the developing analysis will be produced for the core research team, GIDS PPI groups, external PPI advisory group, and clinicians to ensure relevance to family and service development priorities. Procedurally the analysis will draw on the framework method, a widely used approach that is suited to working with large qualitative datasets and facilitating the involvement of multi-disciplinary teams in the analysis (28). Data management and analysis will be assisted by a mixed methods software package.

8 STUDY SETTING

The study will take place at the UK Gender Identity Development Service for children and young people and their families. This is the largest such service in the world and, combined with the increase in referrals in recent years, means that it is uniquely positioned to undertake research of this kind.

9 SAMPLE AND RECRUITMENT

9.1 Eligibility Criteria

Eligibility for participation will be determined by 1) referral status; and 2) age.

9.1.1 Inclusion criteria

In order for children and young people to take part in the study, they must:

- Be aged 3-13 years at the time referral was accepted;
- Have been referred to the GIDS and awaiting their initial appointment prior to first contact;
- Have parental consent;
- Speak English;
- Live in the UK.

9.1.2 Exclusion criteria

Children and young people will not be allowed to participate in the study, should they:

- Be aged 13 years or older at the time of referral;
- Refuse to assent to take part, or not have parental consent;
- Not meet the above inclusion criteria

9.2 Sampling

9.2.1 Size of sample

a) Quantitative study

A total of 638 children and young people will be recruited to the study. This target is based on recruiting 70% of anticipated referrals to the GID service of children and young people age 13 years or under over an 18 month period. Of an estimated total of 3,298 referrals to the service in 18 months, 912 referrals pertained to children and young people aged 13 years or younger in 2016-2017. Allowing for 20% attrition and assuming 40% prevalence of GD (29) a total of 204 GD events are expected to be observed in the 510 children with complete follow-up in the cohort study. This will allow us to fit a logistic regression model with the 14 explanatory variables and estimate the resulting 19 regression coefficients with adequate precision (30). The sample size of 510 will also allow us to estimate the proportion of children with GD, expected to be 40% with reasonable precision 95% CI (35.75% to 44.25%). The proportion receiving physical intervention is anticipated to be around 21% during the follow up time and this proportion can be estimated with a 95% CI (17.45% to 24.55%) (31).

b) Qualitative study

We will purposively sample a sub-set of up to 40 families (children and young people and parents) from the quantitative study for the qualitative baseline interviews. We anticipate that a sample of this size will be necessary to achieve data saturation within sub-samples of interest, particularly to include children and young people who continue to experience gender dysphoria and progress to physical

treatments, as well as to include those who do not progress to physical treatments. Sampling to the qualitative study baseline interviews will cease when saturation and adequate information power (32) is judged to have been reached.

9.2.2 Sampling technique

a) Quantitative study

All children and young people aged 3-13 years when their referral was accepted by the GID service and awaiting a first appointment will be invited to participate in the study. This includes those currently sitting on the waiting list (n=585) and consecutive new referrals to the service (n~43 p/m) across the 18 month recruitment period. The waiting period will be divided into thirds and research effort equally extended on each third. In this way, we shall strive to treat each interval of waiting equally. Our revised strategy will be reviewed regularly and adapted should there be any change in policy towards, or service throughput of, this age group.

b) Qualitative study

Purposive sampling to the qualitative study will be informed by data from the quantitative study. A key aim is to interview CYP who subsequently go on to experience continuing gender dysphoria and progress to physical treatments, as well as CYP whose gender identity issues subsequently resolve and who do not progress to physical treatments. As these outcomes will not be known at baseline, sampling will take account of factors considered to be associated with these outcomes based on current research evidence and clinical knowledge. To address this we will sample equal numbers of CYP who have socially transitioned at baseline and equal numbers who have not socially transitioned at baseline, although we will review this strategy in the light of new evidence emerging over the course of baseline sampling. Across the whole sample we will aim to interview approximately 12 CYP with co-occurring ASD reflecting the large numbers of such CYP referred to GIDS, and approximately 6-8 black and ethnic minority CYP reflecting the UK general population. Sampling will also aim for balance in family socio-economic status, location of GIDS and assigned gender at birth. Sampling will also be informed by the ongoing analysis of both the quantitative study data and qualitative data on an iterative basis.

9.3 Recruitment

9.3.1 Sample identification

a) Quantitative study

Potential participants will be identified from a list of referrals received at the service. Following a request for specific information, a member of the Trust's informatics team will go through a referral list received at the service to source those aged 13 and under at the time their referral was accepted by GIDS and who are currently awaiting their first appointment. They will not need special permissions as they would routinely access this data.

b) Qualitative study

The quantitative assessments will commence prior to the qualitative study. All families will be asked to consent to be approached for participation in the qualitative study at the point of consent for the quantitative assessments. Consent to being contacted for the qualitative study, at the time of consenting for participation in the quantitative study, will be optional. The research assistants working on the quantitative study will share the details of all participants who consented to be contacted for the qualitative study with the qualitative research associate. A sub-set of families (children and young people and their parents) will be identified and recruited to participate from the consents received, as per the above sampling technique. As capacity to take part in an interview is not necessarily dependent upon age, we will explore whether children and young people display Gillick competence at the time of interview. Those who display such capacity will be asked to provide informed consent.

9.3.2 Consent

It is the responsibility of the Investigator, or person delegated by the Investigator to obtain written informed consent from each participant (or assent from their personal consultee) prior to participation in the trial. The informed consent process will be conducted by the research assistants/research coordinator, who will be GCP trained, suitably qualified and experienced in assessing capacity and will have been delegated this duty by the CI or PI on the delegation log. Participants will be given at least 24 hours to consider participating in their first assessment and given the opportunity to ask any questions. It will be explained to the participant that they are under no obligation to participate in the trial and that they can withdraw at any time during the trial without having to give a reason. For the majority of participants for whom data collection will be carried out remotely and electronically, an e-consent procedure will be employed. This will involve participants/ caregivers verbally confirming they are happy to take part in the study and this will be reflected on Red Pill as a tick box for both children and caregivers. For the minority of participants for with whom in-person data collection is carried out, a hard copy of the signed informed consent form will be shared with the participant. The

original signed form will be retained in the investigator site file (ISF) and a copy in the medical/case notes/source documents.

If the PIS and consent form are amended during the trial, participants will be informed of the changes and will be re-consented as appropriate.

a) Quantitative study

Consent will consist of a three-step process. 1) Potential participants (children and young people and their families) will firstly receive a study invitation letter (please see Appendix 6) informing them of the study and inviting them to take part. This letter will, where possible, be included with the child or young person's referral acknowledgement letter sent by the GID service as standard procedure. 2) At least 72 hours after the letter is sent, the child or young person and their family will be contacted by telephone by a member of the GIDS team with responsibility for referrals as part of their duties. The purpose of this telephone call is to highlight the study to potential participants and seek their consent in passing on their contact details to the research team. 3) Should potential participants be happy for their contact details to be forwarded to the research team, a researcher will contact them to share the information sheets, talk through the study and schedule a time for a baseline assessment.

Informed consent will be requested at baseline assessment prior to participation from all caregivers. The majority of assessments will be carried out electronically via Red Pill and guided by the researchers either over the phone or on video call (ie. telemedicine). Consent will be requested and recorded online on the Red Pill database. Caregivers will be re-assessed for capacity to consent verbally by telephone or video calls at follow-up. In a minority of participants, who do not have access to technology or where there are difficulties with technology, we will record consent on paper (at baseline) and conduct assessments in-person.

All children and young people will be asked to assent throughout the study. Under common-law in England those aged 18 years or older are regarded as adults, but we understand that some of our participants may display Gillick competence to consent at a younger age. We have sought guidance on this issue from our sponsor's representative, HRA guidelines, and the research literature in relation to age of consent for minors' participation in research. Although capacity to consent is not dependent on age, these sources displayed a general consensus that individuals aged 16 years or older are likely to be able to consent. In this study, however, we will ask for ethical permission to assent all children and young people for two reasons: 1) only a minority of young people in the study will have reached the age of 16 at the final follow-up assessment, and 2) consenting this small group will require that the

researcher(s) check all participants' date of births, contact those who are over the age of 16 to assess whether they have capacity to consent, and subsequently contact Red Pill to issue a consent form (if required). As the study aims to recruit 638 families and assess these at three separate time-points, time constraints are likely to make this unfeasible.

Please see Appendix 6 for copies of all information sheets, consent and assent forms for the quantitative arm of the study.

b) Qualitative study

Participants will be invited to partake in an interview following their participation in a baseline assessment. At baseline assessment, participants will be asked whether they agree to be contacted to participate in an interview. An information sheet will be provided to all participants at interview. Informed consent will be required prior commencing all interviews. Please see Appendix 7 for copies of information sheets, consent and assent forms for the qualitative arm of the study.

10 ETHICAL AND REGULATORY CONSIDERATIONS

This research is subject to review by the Health Research Authority for HRA Approval and the NHS Research Ethics Committee for REC Favourable Opinion.

10.1 Assessment and management of risk

Senior clinicians experienced in managing safeguarding issues will provide supervision and training to all research assistants. Research assistants who are recruited to the study will have demonstrated strong empathy skills and, following training, will possess an understanding of the potential difficulties experienced by gender diverse children. In addition, research assistants will receive ongoing supervision regarding their interactions with participants, which will incorporate any feedback received by the team about the conduct of research assistants from participants themselves.

Participants may, at times, become distressed during assessments and/or interviews. Should a participant become distressed during either, they will be asked if they would like to take a break or discontinue the assessment/interview. At the conclusion of each assessment or interview, the researcher will debrief with the participant to check how they are feeling. In the event that a participant

becomes significantly distressed or discloses suicidal intent or another significant event that places them at risk, the researcher will inform the GID clinician on-call via the GID enquiries rota immediately after the assessment/interview. Please see the risk protocol (Appendix 8) for more information.

Interviews, and a minority of assessments, are likely to take place within the family home. We acknowledge that home interviews may pose a potential risk to staff. All staff will be required to wear a portable Identicom safety alarm. This alarm has a panic button that directly alerts both the alarm company, and subsequently, the researcher coordinator/PI or agreed contact, when pressed. All researchers will also be asked to let the research coordinator know when they are entering and leaving the site of an interview.

10.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a London REC for the study protocol, informed consent forms and participant information sheets. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the 12-month anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

Should the study end prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

If an amendment to the protocol is necessary, the Chief Investigator will consult with the sponsor for an opinion on whether it should be considered a minor or a substantial amendment for the purposes of the REC. The necessary paperwork and supporting documents will be passed to the sponsor. Amendments will be submitted to the REC for consideration by the sponsor, and to our funding body,

NIHR. If ethical approval for the amendment is granted, the R&D department will be notified of the change(s) by the research team overseen by the Chief Investigator.

All amendments to the protocol shall be tracked in a log at the end of the protocol; a copy of this log will be stored with the current and superseded protocols in the appropriate folder in the Trial Management File.

10.3 Peer review

The study was submitted and successfully received NIHR funding. As part of this screening process, it has undergone extensive peer-reviewed by external peer-reviewers.

10.4 Patient & Public Involvement

The study was developed in collaboration with a service user co-applicant; UK GID service users; and external stakeholders, including voluntary user organisations.

The core research team includes a peer researcher as a co-applicant: a transgender young person and research assistant with both experience of children and young people and Adult GID services and an active interest in research.

Following the NIHR funding call, children/young people and their families using the UK GID service were consulted regarding their priorities for research. At GID Service User Family Days in London (7th August 2017) and Leeds (30th August 2017), the HS&DR funding call was presented and feedback was requested on research questions/priorities families viewed as important, attendees were also asked to complete a short questionnaire. Following the development of the proposal, a draft was shared with three parents of young people accessing the service. Among this group, the major area of interest to emerge in discussion was the need to focus research on the co-occurrence of ASD and GD.

The service has strong links with external stakeholders including voluntary organisations, who have been consulted regarding the proposed research questions and priorities. An external stakeholder event was hosted at the Tavistock on Feb 2nd 2018 bringing together community organisations, youth groups, education and health. Summaries of the research were distributed and the feedback was overwhelmingly positive with many indicating that the proposed research was ‘long overdue’.

Several key service user organisations have indicated their interest and willingness to be represented on the external advisory group and/or provide input to the research. Training will be provided for these advisory group members and they will be paid for time attending meetings (at INVOLVE rates) and reimbursed for travel and additional expenses. Childcare will be provided if required. The external stakeholder advisory group will meet every 6-8 months.

In addition a Children and Young Persons advisory group will meet 6 monthly hosted by the UK GIDS service and Trust PPI (which has developed innovative methods of engaging young people e.g. in 'Pizza and chat' sessions where a local pizza company provides Pizza). A parent advisory group comprised of parents attending the service will meet 6 monthly. Trust PPI has an active well-staffed department that will provide training and support in the running of these groups and will link closely with the research team and GID service. We will ensure BAME representation on all advisory groups and will also link with existing BAME GID user support groups in order to ensure BAME input to the design and conduct of the study.

Funding has been allocated to develop a study website and multi-media resources which will be developed in consultation with key stakeholders and will aim to convey, in a child and family centred way, the 'human stories behind the figures'. Such resources will also assist in the education of NHS commissioners and clinicians schools and other relevant service providers and thereby help enhance support for children/young people and their families. PPI groups will be closely involved in the development of these resources and other activities and events.

10.5 Protocol compliance

The study will be overseen at each site by the Chief Investigator who will be familiar with the study protocol. Researchers already have appropriate experience in conducting research, and will receive the necessary training and supervision in order to carry out the research in each stage as per the protocol. All protocol breaches will be recorded using the appropriate documentation and reported to the Chief Investigator and Sponsor immediately.

Where a deviation from the protocol is reported on more than one occasion, the Chief Investigator and the Sponsor will liaise to investigate the reason for the breach, and suggest changes to ensure that it

does not recur. Should the change require an amendment to the protocol, an application will be made to the REC.

10.6 Data protection and patient confidentiality

a) Quantitative study

Personal data provided during assessments will be pseudonymised and not be used or disclosed in any form that might identify the participant. Pseudonyms will be held in a password protected database on an encrypted NHS server at the Tavistock and Portman NHS Foundation Trust, accessible solely to the chief investigator and immediate research team.

The online database used for quantitative assessments will be prepared for electronic use by the PRIMENT Clinical Trials Unit with technical support from *Sealed Envelope,* an independent company which provides *Red Pill*, a secure online data management system that collects and manages data in partnership with PRIMENT's data management team. All access will be via encrypted channels and limited to the research teams. Sealed Envelope is registered as a data controller with the UK Information Commissioner's Office (ICO) and has been inspected by the MHRA, the UK clinical trials regulator. Sealed Envelope has been assessed by PRIMENT to ensure that adequate processes are in place and are being followed for quality management, software development and security. There will be an agreement in place between UCL and Sealed Envelope to ensure compliance and agreement with clinical trial regulations and data protection laws.

A Data Protection Impact Assessment was carried out on the study assessing identified risks, likelihood of harm, severity of harm, mitigation and overall risk. Information with regards to the study participants will be kept confidential and managed in accordance with the GDPR, NHS Caldicott Guardians, Research Governance Framework for Health and Social Care and the Research Ethics Committee approval.

Analysis of assessment data will be carried out by the UCL PRIMENT team. PRIMENT is composed of experts in both statistical analysis and handling very sensitive data (they are one of the main centres for clinical trial handling at UCL-Royal Free). The 'Statistician' role on the Red Pill database will be used to download data directly from *Red Pill* for analysis.An 'Archivist Role' has been created on Red Pill that allows complete data downloads for ongoing studies for disaster recovery and database closure purposes. Red Pill archives contain data in csv, Stata and MySQL script formats. They also contain

audit logs, a data dictionary and a log of which users have been assigned permission to the Red Pill database whilst in use. Data is downloaded on a monthly basis by PRIMENT as part of the unit's back-up processes. Access is secured via an institutional firewall and restricted to authorized members of the research team. A Data Processing Agreement has been set up between the Trust and UCL and is currently undergoing authorisation.

b) Qualitative study

All digital data files (including audio files) will be assigned a pseudocode and uploaded onto a secure NHS server as soon as possible after data is collected, and the files deleted from the audio recorder memory disk or hard drive. Memory disks and hard drives containing data will be held in locked cabinets if it is not possible to upload the files immediately following data collection. The names of people and/or places mentioned during the interviews will be removed from transcripts before analysis and storage.

Pseudonyms/identity codes will be held in a password protected database on an encrypted NHS server at the Tavistock and Portman NHS Foundation Trust. Audio recordings will be transferred to a trusted transcription company using secure data transfer methods for transcription. Only the Chief Investigator and researchers will have access to assessments and audiorecordings. All members of the research team will be reminded of their duty to observe the NHS code of ethics regarding patient confidentiality. Monitors and auditors from the sponsor and regulatory authorities will have access to the participants' personal data if required. This is detailed in the subject information sheet and consent for this will be obtained from the participant.

10.7 Indemnity

As the Tavistock and Portman NHS Foundation Trust will act as sponsors, indemnity is provided through NHS schemes under Clinical Negligence Scheme for Trusts (CNST). Insurance or indemnity for the design of the protocol will be provided through NHS schemes (CNST).

10.8 Access to the final study dataset

The Chief Investigator and researchers including statisticians and health economist will have access to the final full dataset. Any other person wishing to have access to the full dataset must submit a formal request to the Chief Investigator for approval.

11 DISSEMINIATION POLICY

11.1 Dissemination policy

Intellectual property rights relating to the data arising from the study shall be held by the Tavistock & Portman NHS Foundation Trust.

Following the completion of the studies, data will be meticulously analysed. Findings will be tabulated and detailed in publications.

NIHR will be informed about all outputs resulting from the funded project at least 28 days prior to publication.

Consent to publish study data may be granted to co-investigators by the Tavistock & Portman NHS Foundation Trust.

All dissemination arising from the study must contain details of NIHR as the funder of the study, along with the standard disclaimer.

Participants who consent to receive the study findings will be sent an electronic or hard copy interim report and a final lay summary of the findings, depending on their preferred method of communication. They will also be provided with the details of where to access the online publication of the full study report.

11.2 Authorship eligibility guidelines and any intended use of professional writers

In partnership with the core study team of co-applicants, the Chief Investigator will make the decision regarding authorship for any peer-reviewed articles. All authors will be individually named.

12 REFERENCES

1. Fuss J, Auer MK, Briken P. Gender dysphoria in children and adolescents: A review of recent research. Current Opinion in Psychiatry. 2015;28(6):430-4.
2. De Vries AL, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. Journal of homosexuality. 2012;59(3):301-20.
3. Olson J, Garofalo R. The peripubertal gender-dysphoric child: puberty suppression and treatment paradigms. Pediatric annals. 2014;43(6):e132-e7.
4. Giovanardi G. Buying time or arresting development? The dilemma of administering hormone blockers in trans children and adolescents. Porto Biomedical Journal. 2017;2(5):153-6.
5. Spack NP, Edwards-Leeper L, Feldman HA, Leibowitz S, Mandel F, Diamond DA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. Pediatrics. 2012;129(3):418-25.
6. Connolly MD, Zervos MJ, Barone II CJ, Johnson CC, Joseph CL. The mental health of transgender youth: Advances in understanding. Journal of Adolescent Health. 2016;59(5):489-95.
7. Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: Demographics and associated difficulties. Clinical child psychology and psychiatry. 2016;21(1):108-18.
8. Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. The Journal of Pediatrics. 2014;164(4):906-11.
9. Olson J, Schrager SM, Belzer M, Simons LK, Clark LF. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. Journal of Adolescent Health. 2015;57(4):374-80.
10. Wallien MS, Swaab H, Cohen-Kettenis PT. Psychiatric comorbidity among children with gender identity disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2007;46(10):1307-14.
11. Butler G, De Graaf N, Wren B, Carmichael P. Assessment and support of children and adolescents with gender dysphoria. Archives of Disease in Childhood. 2018;103(7):631-6.
12. Olson-Kennedy J, Cohen-Kettenis PT, Kreukels BPC, Meyer-Bahlburg HFL, Garofalo R, Meyer W, et al. Research Priorities for Gender Nonconforming/Transgender Youth: Gender Identity Development and Biopsychosocial Outcomes. Current opinion in endocrinology, diabetes, and obesity. 2016;23(2):172-9.
13. Butler G, Wren B, Carmichael P. Puberty blocking in gender dysphoria: suitable for all? : BMJ Publishing Group Ltd; 2019.
14. Bradbury-Jones C, Taylor J, Herber O. How theory is used and articulated in qualitative research: Development of a new typology. Social Science & Medicine. 2014;120:135-41.
15. Chamberlain K. Methodolatry and qualitative health research. Journal of health Psychology. 2000;5(3):285-96.
16. Levitt HM, Motulsky SL, Wertz FJ, Morrow SL, Ponterotto JG. Recommendations for designing and reviewing qualitative research in psychology: Promoting methodological integrity. Qualitative Psychology. 2017;4(1):2.
17. Clarke NJ, Willis ME, Barnes JS, Caddick N, Cromby J, McDermott H, et al. Analytical pluralism in qualitative research: A meta-study. Qualitative Research in Psychology. 2015;12(2):182-201.
18. Flanagan SM, Greenfield S, Coad J, Neilson S. An exploration of the data collection methods utilised with children, teenagers and young people (CTYPs). BMC research notes. 2015;8(1):61.
19. Fängström K, Salari R, Eriksson M, Sarkadi A. The computer-assisted interview In My Shoes can benefit shy preschool children's communication. PloS one. 2017;12(8):e0182978.

20. Barrow W, Hannah EF. Using computer-assisted interviewing to consult with children with autism spectrum disorders: An exploratory study. School Psychology International. 2012;33(4):450-64.
21. Salmon P, Mendick N, Young B. Integrative qualitative communication analysis of consultation and patient and practitioner perspectives: towards a theory of authentic caring in clinical relationships. Patient education and counseling. 2011;82(3):448-54.
22. Simons L, Lathlean J, Squire C. Shifting the focus: sequential methods of analysis with qualitative data. Qualitative Health Research. 2008;18(1):120-32.
23. Shukla N, Wilson E, Boddy J. NOVELLA Working Paper: Narrative Research in Action. 2014.
24. Gubrium JF, Holstein JA. Handbook of interview research: Context and method: Sage Publications; 2001.
25. Moran-Ellis J, Alexander VD, Cronin A, Dickinson M, Fielding J, Sleney J, et al. Triangulation and integration: processes, claims and implications. Qualitative research. 2006;6(1):45-59.
26. Calman L, Brunton L, Molassiotis A. Developing longitudinal qualitative designs: lessons learned and recommendations for health services research. BMC medical research methodology. 2013;13(1):14.
27. Creswell JW, Klassen AC, Plano Clark VL, Smith KC. Best practices for mixed methods research in the health sciences. Bethesda (Maryland): National Institutes of Health. 2011;2013:541-5.
28. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC medical research methodology. 2013;13(1):117.
29. Steensma TD, McGuire JK, Kreukels BPC, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: A quantitative follow-up study. Journal of the American Academy of Child & Adolescent Psychiatry. 2013;52(6):582-90.
30. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. Journal of clinical epidemiology. 1996;49(12):1373-9.
31. Machin D, Campbell M, Beng Tan S, Huey Tan S. Sample Size Tables for Clinical Studies, Third Edition. Oxford, UK: Wiley-Blackwell; 2009.
32. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. Qualitative health research. 2016;26(13):1753-60.

13. APPENDICES

Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	18.07.2019		All sections that refer to the sample; which has been amended to 3-12 year olds at age of referral across the entire referral waiting list. Sections most extensively changed are: 9.1.1 (Inclusion criteria), 9.1.2 (Exclusion criteria), 9.2.2 (Sampling technique), and 9.3.1 (Sample identification). REC & HRA approval granted 29.08.2019
2	2.1	18.07.2019		Changes to sections 9.3.1 (sample identification) and 9.3.2 (consent stages), both in relation to how participants are identified and who contacts participants in the quantitative study. REC & HRA unfavourable opinion given 27.08.2019
3	2.2	16.09.2019		All sections that refer to the sample; which has been amended to 3-13 year olds at age of referral across the entire referral waiting list. Sections most extensively changed are: 9.1.1 (Inclusion criteria), 9.1.2 (Exclusion criteria), 9.2.2 (Sampling technique), and 9.3.1 (Sample identification).

Appendix 2 – Proposed timeline (please see attached document)

Appendix 3 – Table of procedures and measures

Intervention or procedure	Total no. of interventions or procedures	Average time taken per intervention or procedure	Who will conduct intervention or procedure
Information provision by phone (all appropriate referrals)	1	10 mins	GIDS team member
Information provision by phone (families agreed to be contacted)	1	20 mins	Appropriately trained researcher at Tavistock & Portman
Questionnaire assessment for all parents/carers completed at T0, T1 and T2:	3	40 - 60 mins	Self-report

- **Demographics/Background** (Parent age; Parent gender identification; Parent employment status; Parent education level; Parent ethnicity; Parent sexual orientation; Child age; Child birth assigned sex; Child ethnicity; Family living situation; Household composition; Marital status) - **Child Gender Questionnaire for Parents** (DSM Criteria for Gender Dysphoria; Gender Identity; Background to Referral; Social Transition; Body Image & Distress) - **Strengths & Difficulties Questionnaire** (SDQ; Brief Emotional and Behavioural Screener) - **Child Behaviour Checklist** (CBCL; Emotional and Behavioural Functioning) - **Autism Quotient** 50 item scale (AQ; Child (age 4-11) or Adolescent (age 12-15) version; Autism Traits) - **Child and Adolescent Service Use Schedule** (CA-SUS; Health care resource use) Questions relating to healthcare resource use will be adapted by Rachael Hunter (Health Economist)			
Additional questionnaire assessment for parents/carers of children who are under 12, or refuse to participate but agree to parent/carer participating, or are lacking capacity complete self-report measures at T0, T1, or T2: - **Kidscreen 52** items-parental proxy (KIDSCREEN-52; Child health and well-being)	Dependent on age/competence of child at each time point (between 0 and 3)	20 mins	Parent proxy report

- **Child Health Utility 9 Dimensions** - parental proxy (CHU-9D; Quality of life)			
Interview and guided assessment for children aged 3-11 years with capacity to participate at T0, T1, or T2: - **Children's Gender Identity Semi-Structured Interview** - **Gender Similarity Task** - **Child and Youth Resilience Measure** (CYRM) - **Child Health Utility 9 Dimensions** (CHU-9D)	Dependent on age/competence of child at each time point (between 0 and 3)	60 mins	Self-report
Questionnaire assessment for children over 12 years with capacity to self-complete at T0, T1, or T2: - **Gender dysphoria questionnaire** (GDQ) - **Young Persons Gender Questionnaire** (DSM Criteria for Gender Dysphoria; Gender Identity; Background to Referral; Social Transition; Body Image & Distress; Relationships & Attraction) - **Utrecht Gender Dysphoria Scale** (UGDS; Gender Dysphoria Scale\) - **Strengths and Difficulties Questionnaire** (SDQ; brief emotional and behavioural screener) - **Moods and Feelings Questionnaire** (MFQ; depressive symptoms) - **Child and Youth Resilience Measure** (CYRM; social-ecological resilience) - **Gender Identity Self Stigma Scale** (internalised stigma and transphobia) - **Kidscreen 52 items** (KIDSCREEN-52; Child health and well-being)	Dependent on age/competence of child at each time point (between 0 and 3)	60 mins	Self-report

- **Warwick-Edinburgh Mental Wellbeing Scale** (WEMWBS; Mental wellbeing) - **Child Health Utility 9 Dimensions** (CHU-9D; Quality of life) - **Youth Self Report** (YSR; Emotional and Behavioral Functioning)			
Physiological assessment for <u>all</u> participants, including those not going to a clinic: - Parents heights (at start) - Child's height - Child's weight - Child's pubertal development (RCPCH guidance on measuring puberty phase) - BMI All of the above are self-measured or measured with assistance from a parent/carer at each assessment (T0, T1, T2) using simple instructions provided by research team	3	5 – 10 mins	Self-measured
(Request for routinely collected data – not part of intervention research) Physiological assessment for participants (children and young people) receiving physical treatment with hormone blockers (GnRH agonists) and/or cross-sex hormones: - Parent's heights (Clinical measure) - CYP height, sitting height, bi-acromial width, bi-iliac width, weight (clinical measures) - BMI (value derived by calculation) - Pubertal Tanner staging (Clinical examination)	3	N/A	University College London Hospitals (UCLH) NHS Foundation Trust

- Body composition (Tanita bioelectrical impedance analyser) Radiological measures - Bone densitometry (Dexa Scan) - Bone age (X-ray of left hand & wrist) General blood and endocrine measures - Full blood count, ferritin (iron) - Renal, liver, lipid and bone profiles - Vitamin D - Thyroid function - Reproductive hormones (FSH, LH, PRL, Testosterone, Oestradiol)			