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

FULL/LONG TITLE OF THE STUDY

Longitudinal Outcomes of Gender Identity in Children (LOGIC): A secondary analysis

SHORT STUDY TITLE / ACRONYM

LOGIC: Secondary Analysis

PROTOCOL VERSION NUMBER AND DATE
Protocol 1.2 25/02/2019

RESEARCH REFERENCE NUMBERS

IRAS Number:	257122
SPONSORS Number:	K-624-1203
FUNDERS Number:	HS&DR 17/51/19

LIST of CONTENTS

STUDY SUMMARY.

Study Title	Longitudinal Outcomes of Gender Identity in Children (LOGIC): A secondary analysis
Internal ref. no. (or short title)	LOGIC: Secondary Analysis
Research Questions/Aims	1. What is the profile of children and younger adolescents referred to UK and Dutch GID services? 2. What proportion of children and younger adolescents, aged 0-13 years, referred to these services 1) socially transition; 2) go on to have physical treatment; and 3) have traits of co-occurring Autism Spectrum Disorder? 3. Do the profiles of those who attend the paediatric endocrinology clinics in the UK and the Netherlands (as part of the GID services) differ from those who do not attend? 4. What is the service use and cost inferred by these CYP clinics? 5. Is there a relationship between the costs of the service and the outcomes of CYP that attend the paediatric endocrinology clinics, and do these differ between the UK and the Netherlands?
Study Participants	Children and young people (CYP) referred to GID clinics in the UK and Netherlands.
Planned Size of Sample (if applicable)	The clinical carenotes database holds records on 557 children and young people in the UK and 1,202 children and young people in the Netherlands for 2009-2017.
Follow up duration (if applicable)	N/A
Planned Study Period	18 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 FINANCIALSUPPORT GIVEN**
NIHR	£ 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 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

As part of the larger longitudinal study, a Study Steering Committee (SSC) which will include an independent chair, PPI representation, independent clinicians and academics, will meet 6 monthly and will report to NIHR HS&DR and the sponsor. Regular reporting to NIHR will be undertaken as required. There will be ongoing communication (6-8monthly) with 'internal' PPI advisory groups (parents and CYP attending the GID service) and an 'external' Stakeholder advisory group (external user organisations). The SSC will include representation and feedback from these PPI advisory groups.

KEY WORDS: Secondary analysis; Gender dysphoria; Gender identity; Children and Young People

STUDY TIMELINE (please see Appendix One)

STUDY PROTOCOL

Longitudinal Outcomes of Gender Identity in Children (LOGIC): A secondary analysis

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 including in the UK where, for example, referrals increased from 97 a decade ago to 2,519 in 2017/18. In addition to this rise in overall number of referrals, age at the time of referral has also dropped over the last decade (2, 3) and the number of younger children in UK services accessing physical treatments is rising (4). Recent referral data have also shown a change from a predominance of birth assigned males (AM) to more birth assigned females (AF), with corresponding patterns in other countries (5, 6).

While not all gender-diverse CYP 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 further associated with a range of negative mental and physical health difficulties, including depression, anxiety, suicidality and substance abuse (7-12). Current NHS intervention for children and young people (CYP) 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. However, the evidence base on which the current treatment protocols are based is widely acknowledged to be both limited and shifting (13). To date, no information exists which can be used clinically for predicting individual gender and psychosexual developmental pathways (12). It is difficult to predict what proportion of younger pre and peri-pubertal CYP referred to NHS services will later access physical treatment with GnRH (Gonadotropin-releasing hormone) agonists 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.

The proposed research aims to provide an in-depth characterization of children and younger adolescents, aged up to 13 years, presenting to both the UK and Dutch Gender Identity and Development Services. In

doing so, we aim to develop a greater understanding of the heterogeneity and individual differences within the referred population of CYP so that more tailored assessment and support can be developed.

2 RATIONALE

A particular gap in the evidence both in the UK and internationally relates to children/younger adolescents presenting to services for which there is minimal research evidence to inform questions regarding likely trajectories and outcomes. Very little is known overall about the profile of children and younger adolescents referred to GID services. This group is poorly characterised compared to older adolescents referred. Major knowledge gaps 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). Therefore, this secondary analysis will analyse routinely collected data on these characteristics to help generate important knowledge regarding patient outcomes overall. It will also inform us about treatment costs and outcomes and will identify potential differences between those who choose to undertake physical treatment and those who do not.

3 RESEARCH QUESTION/AIM(S)

1. What is the profile of children and younger adolescents referred to UK and Dutch GID services?
2. What proportion of children and younger adolescents, aged 3-13 years, referred to these services 1) socially transition; 2) go on to have physical treatment; and 3) have traits of co-occurring Autism Spectrum Disorder?
3. Do the profiles of those who attend the paediatric endocrinology clinics in the UK and the Netherlands (as part of the GID services) differ from those who do not attend?
4. What is the service use and cost inferred by these CYP clinics?
5. Is there a relationship between the costs of the service and the outcomes of CYP that attend the paediatric endocrinology clinics, and do these differ between the UK and the Netherlands?

3.1 Objectives

Our objectives are to:

1. Undertake a retrospective analysis of referrals of CYP age 13 and under to GID services in the UK and Holland;

2. Establish retrospectively (over 8 years) the proportion of CYP referred at age 13 and under who a) socially transition b) choose physical treatment c) have co-occurring ASD;
3. Establish retrospectively (over 8 years) the number of CYP age 13 and under in each country who go on to attend the Paediatric Endocrinology Clinic and compare with CYP who do not attend the Paediatric Endocrine Clinic;
4. Establish retrospectively (over 8 years) from the Clinic Database in each country the resources and cost of the care pathway for CYP that attend the Paediatric Endocrinology Clinic and those that do not;
5. Conduct an analysis of the relationship between care pathway costs and outcomes in each country for CYP that attend the Paediatric Endocrinology Clinic and those that do not.

3.2 Outcome

The study will provide valuable new data for GID services on the factors that influence costs and outcomes in health service delivery for gender diverse children and young people and their families. It will be key to planning new and modified services which might better meet patients' needs in the most affordable way. It will identify factors explaining why a Child or Young Person continues to experience ongoing distress in relation to their Gender Identity and the factors that influence their mental health, behavioural and emotional functioning and quality of life. Additionally, it will identify the factors that influence whether a CYP chooses physical/endocrine treatment and will 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 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 CYP/family characteristics. This new knowledge will be used to: a) better inform patients and their families b) develop improved interventions for CYP and their parents c) more effective and cost effective services. We shall disseminate our findings through diverse and innovative methods including state of the art social media engagement that targets 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). 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 significantly enhanced 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 CYP and their families. A common data set of measures will be developed for use in services and there will be a clearer understanding of what determines good outcomes as well as the outcomes that matter to CYP and their families.

4 THEORETICAL FRAMEWORK

This secondary analysis will not employ a theoretical framework. It will seek to answer the research questions listed above.

5 STUDY DESIGN

The study will consist of a secondary analysis of routinely collected data at two sites: the Gender Identity clinics at the Tavistock & Portman NHS Foundation Trust; and VU Medical University in Amsterdam.

This study will encompass a secondary analysis of demographic, clinical, gender identity-related, and healthcare resource variables. It will include the following factors: 1) age, ethnicity, and registered sex assignation at birth; 2) diagnosis of gender dysphoria; 3) family composition; 4) social transition; 5) school involvement; 6) travel distance to service; 7) gender identity; 8) emotional and behavioural functioning; 9) ASD traits; and 10) type, attendance and frequency of clinical appointments. Differences between clinics, such as time (year) of offering early physical interventions will also be explored and may be adjusted for in the analyses if appropriate. Please see Appendix One for further information regarding the variables.

6 METHODS of DATA COLLECTION

The research teams at each respective site (T&P in UK, and VU in the Netherlands) will submit a request for data extraction to their local informatics team. In the UK, data will be extracted by each informatics team from electronic patient record software ('Carenotes') and entered into a CSV-formatted dataset. Any necessary data that cannot be extracted by the informatics team (such as handwritten or typed data featuring in assessment reports that have been uploaded onto Carenotes) will be manually inputted onto the dataset by the research teams. Individuals' names, aliases, patient IDs and dates of birth will be used solely for the researchers to identify and be able to manually input any data needed from written reports. Once the dataset is complete, all identifiable data will be expunged from the database.

7 METHODS of DATA ANALYSIS

Following extraction and database completion, the database will be anonymised. Once the dataset has been fully anonymised, it will be uploaded and stored on UCL's encrypted data portal, Data Safe Haven. Data Safe Haven is an online storage space compliant with UCL's Information Governance requirements for storing patient identifiable information. The dataset will then be downloaded and analysed by the UCL PRIMENT statisticians and their direct team (RO, MK and UCL-appointed statistical staff).

The characteristics of the CYP in the clinic databases will be described using mean (SD), median (IQ range) or frequencies (proportion) as appropriate. The proportion of children who socially transition, choose physical treatment (i.e. attend the Paediatric Endocrine Clinic) and have co-occurring ASD will be estimated along with their 95% confidence intervals. A descriptive comparison of characteristics will also be made between those who attend the Paediatric Endocrine Clinic and those who do not. All results will be presented by country and also combined. Appropriate regression models will be used to examine factors that influence the number and type of contacts with services by children and young people.

To establish healthcare resource costs, data pertaining to individual appointments (ie. standard appointment; outreach appointment; endocrine clinic appointment) from the time of referral until discharge from the service will be analysed. For our main analysis, we will follow Dutch guidelines to attach costs to health care resource use (https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen/richtlijnen-voor-economische-evaluatie). These will be converted to British Pounds using the relevant purchasing power parity exchange rate. A sensitivity analysis will investigate the impact of costing Dutch resource use using published English NHS costs. Clinic appointments will then

be multiplied by published unit costs in each country to calculate the total cost of care for each CYP. Average costs and appointments will be reported by CYP that attended a CYP Paediatric Endocrinology Clinic versus those that did not. This will be reported for the UK and Netherlands separately. We hypothesise that the GID care pathway for patients that 1) attend the Paediatric Endocrinology Clinic will be more expensive than for patients that do not attend but that this increased cost will be offset by improved mental health and wellbeing outcomes for those young people and their families that have been facilitated in making an individualised decision through an adequately resourced care pathway. 2) Conversely, the costs of helping those young people and their families who make an individualized choice *not* to opt for endocrine treatment, will be offset by the reduction in the physical health care costs that would have accrued from such an intervention. Outcomes for CYP will be examined in relation to psychological health and ongoing Gender Dysphoria. Furthermore, we will conduct an analysis that will include (i) costs of care; (ii) country of care; (iii) care pathway; (iv) outcomes including well-being; and (v) potential predictors of costs and outcomes.

8 STUDY SETTING

Data pertaining to the Gender Identity Clinic at the Tavistock & Portman NHSFT will be extracted from the Tavistock & Portman NHSFT's electronic patient record software ('Carenotes') and will be uploaded onto UCL's encrypted data portal and storage space 'Data Safe Haven'. Data pertaining to the Gender Identity Clinic at the VU University Medical Centre in Amsterdam will be extracted at VU University Medical Centre in Amsterdam and will be forwarded to the Tavistock & Portman research team in a fully anonymised format. The data extracted from both sites consists of routinely collected data by their respective gender identity clinics. Once all data is inputted onto the online database, it will be downloaded and held by UCL for the purposes of analysis. Once analysis has been completed, the Tavistock & Portman NHSFT will request that both UCL and the online database be destroyed. The Tavistock & Portman NHSFT will securely hold the data in accordance with the GDPR.

9 SAMPLE AND RECRUITMENT

9.1 Eligibility Criteria

The sample will consist of data from all children and young people aged 0-13 years who attended a gender identity clinic either at the Tavistock & Portman NHSFT or VU University Medical Centre in the Netherlands, for gender dysphoria in the time period 2009-2017.

9.1.1 Inclusion criteria

Previous attenders' data will be included in the secondary analysis if they meet the following criteria:

- Attended a gender identity clinic through the Tavistock & Portman NHSFT, or VU University Medical Centre in the Netherlands, for gender dysphoria in the time period 2009-2017.
- Aged between 0-13 years in that time period.

9.1.2 Exclusion criteria

Previous attenders' data will be excluded for the secondary analysis if they were aged 14 years or older when they attended a gender identity clinic either at the Tavistock & Portman NHSFT or VU University Medical Centre in the Netherlands, for gender dysphoria in the time period 2009-2017.

9.2 Sampling

The sample will consist of routinely collected data for all attendees aged 0-13 years who attended a gender identity clinic either at the Tavistock & Portman NHSFT or VU University Medical Centre in the Netherlands, for gender dysphoria in the time period 2009-2017.

9.2.1 Size of sample

A total of 1,759 children and young people's data will be entered into the database for analysis. This includes 557 children aged 0-13 years who sought treatment at the Tavistock & Portman NHSFT in the UK, and 1,202 children aged 0-13 years who sought treatment at VU University Medical Centre in the Netherlands, during 2009-2017.

9.2.2 Sampling technique

Data for all attendees aged 0-13 years at a gender identity clinic either at the Tavistock & Portman NHSFT or VU University Medical Centre in the Netherlands, for gender dysphoria in the time period 2009-2017, will be included. No sampling technique will be used.

9.3 Recruitment

There will be no recruitment to the study. The study will be a retrospective secondary analysis of data already routinely collected by the services.

9.3.1 Sample identification

The sample will consist of routinely collected data for all attendees aged 0-13 years who attended a gender identity clinic either at the Tavistock & Portman NHSFT or VU University Medical Centre in the Netherlands, for gender dysphoria in the time period 2009-2017.

9.3.2 Consent

Consent will not be sought from participants. The data is routinely collected from the services and will be analysed for health or social care purposes; public health purposes; archiving in the public interest, scientific or historical research purposes or statistical purposes; and for reasons of substantial public interest.

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

Clinicians at GIDS were involved in the construction of this proposal and continue to be involved in the progress of its evaluation. The UCL PRIMENT team, who will be conducting the statistical analysis of the data, 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). Advice was also sought from the information governance team and Data Protection Officer based at the Tavistock & Portman NHSFT, who are setting up the appropriate Data Processing Agreements. A Data Protection Impact Assessment was carried out on the study assessing identified risks, likelihood of harm, severity of harm, mitigation and overall risk.

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. 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.

If the study is ended 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

Once favourable opinion has been granted by the REC, the research team will apply for permission to conduct the study from the relevant NHS R&D department. The study shall begin only when local R&D approval has been given and the research team have been granted letters of access.

Should any amendment be made to the study that may affect NHS permission, the research team will liaise with the R&D department in order to confirm on-going permission. This includes minor and substantial amendments.

Amendments

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.

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 overall study, of which this secondary analysis is a part of, 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 UCL MSc Psychology student with both experience of CYP and Adult GID services and an active interest in research. Following the NIHR funding call, CYP 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’.
A wide range of external stakeholders will be engaged in the proposed research. The co-applicant peer researcher will be involved in advising and supporting on PPI on an ongoing basis, including social media strategy, stakeholder outreach and the dissemination of study findings. She has an honorary contract with T&P and is on the staff bank so will be appropriately reimbursed for work undertaken as advised by INVOLVE. An external stakeholder advisory group will be recruited to work alongside the

core research team. The terms of reference for this group have been drafted in consultation with INVOLVE and the Trust PPI team and a plan for recruitment of the group is in place. The purpose of the group is to engage a diversity and range of perspectives in order to provide ongoing feedback on the conduct of the research and facilitate the dissemination of study findings. Several key service user organisations have indicated their interest and willingness to be represented on the advisory group and/or provide input to the research. Training will be provided for Advisory group members and group members 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 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 CYP and their families. PPI groups will be closely involved in the development of these resources and other activities and events (such as e.g. stakeholder event held on 2nd Feb bringing together community organisations, health and education).

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 doesn't recur. Should the change require an amendment to the protocol, an application will be made to the REC; R&D departments at each site will be notified of any change following the decision of the REC.

10.6 Data protection and patient confidentiality

The online database will be prepared for electronic use by PRIMENT Clinical Trials Unit. The researchers will upload an anonymised dataset onto the *Data Safe Haven* system. UCL's Data Safe Haven file and storage drives are backed up daily. Access is secured via an institutional firewall and restricted to authorized members of the PRIMENT research team.

Information with regards to the study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardians, Research Governance Framework for Health and Social Care and the Research Ethics Committee approval.

10.7 Indemnity

As 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 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.

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

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. Curr Opin 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. J Homosex. 2012;59(3):301-20.
3. Johanna Olson RG. The peripubertal gender-dysphoric child: Puberty suppression and treatment paradigms. Pediatrics. 2014;43(6).
4. Giovanardi G. Buying time or arresting development? The dilemma of administering hormone blockers in trans children and adolescents. Porto Biomedical Journal. 2017.
5. Aitken M, Steensma TD, Blanchard R, VanderLaan DP, Wood H, Fuentes A, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. J Sex Med. 2015;12(3):756-63.
6. de Graaf, N.M., Carmichael, P.,Steensma, T.D., Zucker, K.J. Evidence for a Change in the Sex Ratio of Children Referred for Gender Dysphoria: Data From the Gender Identity Development Service in London (2000-2017). J Sex Med 2018;15:1381.
7. 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.
8. Connolly MD, Zervos, M. J., Barone, C. J., Johnson, C. C., & Joseph, C. L. The Mental Health of Transgender Youth Advances in Understanding. Journal of Adolescent Health. 2016;59(5):489-95.
9. Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: Demographics and associated difficulties. Clin Child Psychol Psychiatry. 2016;21(1):108-18.

10. Khatchadourian K, Amed S, Metzger DL. Clinical management of youth with gender dysphoria in Vancouver. J Pediatr. 2014;164(4):906-11.
11. Olson J, Schrage 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;57:374-80.
12. Wallien MS, Swaab H, Cohen-Kettenis PT. Psychiatric comorbidity among children with gender identity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46(10):1307-14.
13. Olson-Kennedy J, Cohen-Kettenis PT, Kreukels BP, Meyer-Bahlburg HF, Garofalo R, Meyer W, et al. Research priorities for gender nonconforming/transgender youth: gender identity development and biopsychosocial outcomes. Curr Opin Endocrinol Diabetes Obes. 2016;23(2):172-9.

13. APPENDICES

Appendix 1 – Proposed timeline (please see attached document)

Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
None	1.2	25/02/2019		All instances in which Red Pill was mentioned as our preferred database storage solution have been substituted by Data Safe Haven.