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20-08-2025

Medicines and Healthcare Products Regulatory Agency (MHRA)
10 South Colonnade,
Canary Wharf,
London,
E14 4PU

And

City and East REC Committee

Dear REC Committee, HRA and MHRA,

Re: Request for Clinical Trial Authorisation

Full Title of project: Puberty suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS); **PATHWAYS TRIAL, PATHWAYS CONNECT and PATHWAYS HORIZON INTENSIVE**
Acronym: PATHWAYS TRIAL, HORIZON INTENSIVE, CONNECT
IRAS Number: 1011645
Chief Investigator: [redacted]
Co-sponsors: King's College London, South London and Maudsley NHS Foundation Trust

Please find enclosed our application to conduct the above clinical trial.

The sponsor and I, as Chief Investigator, have authorised this application. The following documents accompany the submission:

Document(s)	Version/Date
Protocol	V1.0 20.08.25
Participant Information Sheets:	
CYP Trial PIS	V1.0 13.08.25
Parent Trial PIS	V1.0 13.08.25
CYP HORIZON Intensive PIS	V1.0 13.08.25
Parent HORIZON Intensive PIS	V1.0 13.08.25

CYP CONNECT (Trial) PIS	V1.0 13.08.25
Parent CONNECT (Trial) PIS	V1.0 13.08.25
CYP CONNECT (HORIZON Intensive) PIS	V1.0 13.08.25
Parent CONNECT (HORIZON Intensive) PIS	V1.0 13.08.25
Informed Consent/Assent Forms:	
CYP Consent for 16+ (Trial)	V1.0 13.08.25
CYP Assent for under 16 (Trial)	V1.0 13.08.25
Parent Consent for under 16 (Trial)	V1.0 13.08.25
CYP Consent for 16+ (HORIZON Intensive)	V1.0 13.08.25
CYP Assent for under 16 (HORIZON Intensive)	V1.0 13.08.25
Parent Consent for under 16 (HORIZON Intensive)	V1.0 13.08.25
CYP Consent for 16+ (CONNECT)	V1.0 13.08.25
Parent Consent for under 16 (CONNECT)	V1.0 13.08.25
GP Letter:	
• TRIAL	V1.0 24.06.25
• HORIZON-Intensive	V1.0 24.06.25
• CONNECT	V1.0 24.06.25
Pharmacy:	
Pharmacy Manual	16.07.2025
IMP Labels	16.07.2025
Validated Measures	
Non-Validated Measures	
Insurance Documents	
Legal Liability for Human Clinical Trials	2025-2026
No Fault Compensation for Human Clinical Trials	2025 - 2026
SoECAT	

PATHWAYS HORIZON INTENSIVE SoECAT	19.08.2025
PATHWAYS TRIAL SoECAT	19.08.2025
Site Documents	
OID Template	12.08.2025
MNCA Template	11.08.2025
Investigator CV	
[redacted] CV	21.02.2025
Funding Letter	
NIHR167530 Funding Confirmation Letter	23.01.2025

The Reference Safety Information (RSI) for the Trial is in section 9.1 of the protocol.

Brief description of study

Background: The study for which we are seeking ethical opinion is supported under that National Research Collaboration Programme, funded by NHS England and scientifically reviewed and monitored by the National Institute for Health and Care Research. The study arises because, in 2024, the UK Parliament passed a law banning the use of puberty suppressing hormones (gonadotropin releasing hormone analogies - GnRHa) for the indication of gender incongruence/gender dysphoria in young people outside of a research context. The law was passed based on the findings of the Cass Independent Review concluding that the evidence base was weak regarding both the benefits and harms of GnRHa for this indication.

This application includes two studies with inter-related participant groups. PATHWAYS TRIAL is a randomised controlled study of GnRHa amongst children and young people with gender incongruence who are deemed clinically eligible for this intervention. The trial will randomise patients to immediate vs delayed (one year) initiation of GnRHa with primary endpoint at two years post randomisation. Patients will be stratified by Gender Service site, birth-registered sex, pubertal (Tanner) stage and presence of neurodevelopmental disorders/high trait levels. The study will recruit participants for 3.5 years and follow them up for the duration of the funding period, with a minimum of 2 years as the primary endpoint. The target sample size is 226 participants. All participants will be patients in one of the new Gender Services and will have received a comprehensive assessment coupled with individualised, non-endocrine interventions addressing their needs. Only once these have been completed will the possibility of endocrine intervention (GnRHa) be considered. The protocol outlines the rigorous multi-professional evaluation of patients who wish to be considered for GnRHa. Only

patients who are considered clinically eligible will be referred to the research team and the research team will not attempt in any way to influence the number of rate of referrals to the trial. This is a pragmatic trial in which the delivery of GnRHa aims to emulate routine clinical practice, were the intervention to become available for this indication in the future. Outcome measures include quality of life (primary outcome), mental and physical health, cognition and gender identity and dysphoria. Adverse effects will be regularly monitored and reviewed, including by Oversight Boards. Data analysis will use a Bayesian approach.

PATHWAYS HORIZON INTENSIVE is a subset of PATHWAYS HORIZON, a study that has already completed ethical and regulatory checks. This participant group is made up of patients not wishing/not eligible for GnRHa. They will be broadly matched to those in TRIAL in order to provide a non-randomised control group of 300 participants. HORIZON INTENSIVE participants will receive the same physical and cognitive measures as those in TRIAL, providing information on the developmental trajectories of these characteristics amongst young people with gender incongruence who do not receive endocrine interventions.

PATHWAYS CONNECT is a study of brain development using magnetic resonance imaging (MRI) amongst young people with gender incongruence. It involves a subset of participants from TRIAL (n=150) PATHWAYS HORIZON INTENSIVE (n=100). The former group participate in MR imaging at 3 timepoints: baseline, mid-point (1year post-randomisation) and primary endpoint (2 years post-randomisation). HORIZON INTENSIVE participants are imaged at baseline and endpoint.

When invoicing us for the application fees, please address the invoice to King's College London and include the PO number [redacted]

We look forward to hearing from you. Please do not hesitate to contact us should you require additional information or clarification.

Yours faithfully,

[redacted]

[redacted]@kcl.ac.uk