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Medicines and Healthcare Products Regulatory Agency (MHRA)
10 South Colonnade,
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And

City and East REC Committee

Full Title of project: Puberty suppression And Transitional Healthcare with Adaptive Youth Services (PATHWAYS); **PATHWAYS TRIAL, PATHWAYS CONNECT and PATHWAYS HORIZON INTENSIVE**
Acronym(s): PATHWAYS TRIAL, PATHWAYS HORIZON INTENSIVE, PATHWAYS CONNECT
IRAS Number: 1011645
Protocol Version: v2.0
Chief Investigator: [redacted]

Dear REC and MHRA

PATHWAYS Response to Grounds for Non-Acceptance

We are providing you with a response to the Grounds of Non-Acceptance for the PATHWAYS Trial. The PATHWAYS Trial is a CTIMP, with an embedded intensive observational study (PATHWAYS HORIZON INTENSIVE) and neuroimaging study (PATHWAYS CONNECT)

Part 1: MHRA Clinical Grounds for Non-Acceptance

There were 19 points related to the clinical GNA. Points 1-19 have been addressed following discussions with [redacted]. The points and accompanying changes made by the PATHWAYS Team are listed below:

1. The language used in inclusion criteria #2 and #6 are open to variable interpretation, could permit premature pharmacological intervention and may allow inconsistency across sites or among investigators. The criteria must be amended as follows:

a. Inclusion criteria #2 - The CYP wants puberty suppression for their gender incongruence and this care preference persists after “completing all” other care deemed appropriate from the CYPGS and other sources.
b. Inclusion criteria #6 - The clinician in the CYPGS leading on care for an individual patient believes that they have participated sufficiently for their holistic health and well-being, “completing all” other forms of “psychosocial/psychological interventions” for puberty suppression to be considered, in line with NMDT recommendations.

Additionally, the criteria used to define the term “participated sufficiently” must be clearly detailed in the protocol.

Answer:
a. Inclusion criterion #2. This is a heterogeneous population of young people who have an individualised assessment and personalised psychosocial treatment plan. Psychosocial interventions may continue following randomisation. The safeguards in place with all CYP being reviewed by the national MDT are extensive and beyond usual care. Wording has therefore been amended to: “The CYP wants puberty suppression for their gender incongruence and this care preference persists after receiving other care deemed appropriate from the CYPGS and other sources prior to the initiation of GnRHa.”
b. Inclusion criterion #6. As highlighted above, there is no specific definition of ‘sufficient participation; for this heterogeneous group. Participation in other interventions will be reviewed by the NMDT for each CYP. Criterion amended to: “The clinician in the CYPGS leading on care for an individual patient believes that they have participated sufficiently for their holistic health and well-being in other forms of care for puberty suppression to be considered, in line with NMDT recommendations and this participation is reviewed by the NMDT.”

2. The inclusion criterion #5 is vague and open to subjective interpretation. Terms such as “possibility”, “may benefit” and “might be achieved” do not provide sufficient clarity to ensure consistent eligibility determination. In accordance with ICH E11(R1), eligibility criteria must be specific enough to define the study population. The inclusion criterion must therefore be revised as follows:
   a. The clinician in the CYPGS leading on care for that CYP believes “the CYP, with persistent gender incongruence despite other appropriate care, is likely to” benefit from GnRHa for puberty suppression. This benefit “is expected to” be achieved in relation to quality-of-life parameters (e.g., confidence in peer and family relations, participation in school and/or leisure activities, improved sense of well-being), mental or physical health.

*Answer: the protocol inclusion criterion has been modified to: “*The clinician in the CYPGS leading on care for that CYP considers that GnRHa for puberty suppression offers a reasonable prospect of benefit. This benefit might be achieved in relation to quality-of-life parameters (e.g., confidence in peer and family relations, participation in school and/or leisure activities, improved sense of well-being), mental or physical health.”

3. The following clinical inclusion criteria must be added in line with GCP requirements:
   a. Willingness of the CYP and parent(s)/guardian(s) to be randomized into either study arm, documented by signed informed consent (parent/guardian) and assent (CYP).

Answer: This has been accepted and added as an inclusion criterion (#9) in the updated protocol.

4. The following clinical exclusion criteria must be added:
   a. Hypersensitivity to GnRH (gonadotropin releasing hormone), its analogues or to any of the excipients
   b. QTc interval > 450 milliseconds at screening.
   c. Known QT prolongation or family history of long QT syndrome.

Answer: Clinical exclusion criteria (section 3.2.1.3) has been updated to include point a regarding hypersensitivity to GnRH. In agreement with the MHRA, clinical exclusion criteria have been added to exclude known congenital long QT Syndrome and baseline QT > 470 ms, or concomitant high-risk QT-prolonging drugs that cannot be stopped. ECG will be obtained at screening on all participants and only at further timepoint where clinically indicated (European Cardiology Review 2017;12(2):112–20 DOI: https://doi.org/10.15420/ecr.2017:16:1)

5. The protocol currently states that longer term follow-up - "in the first instance will be for the life of the funding (total period 5.5 Years)."

While it is acknowledged that funding constraints may not be fully within the sponsor's control, this follow-up duration is inadequate to assess the long-term benefits and risks of the IMPs in the study participants. Identified risks include but not limited to, effect on fertility preservation, bone mineral accrual, fracture risk, cognitive development and sexual function which requires monitoring. Many of these outcomes will only become measurable in adulthood. Therefore, a follow-up for a period of up to 20 years or until the participant reaches the end of physical maturation (whichever is shorter) is deemed necessary.

The sponsor is required to address the following:

- 5.1. The protocol must be amended to include the necessary long-term safety monitoring either by extending the formal follow-up period in this study, or through a separate safety long-term extension study. Alternatively, the sponsor must provide a scientific rationale, supported by clinical data, to justify the lack of long-term safety monitoring.
- 5.2. References to study funding should be confined to section 15.5 (Funding) and removed from the sections on trial design, objectives, safety monitoring, and the schedule of events. Funding is an operational element of the study, and it should not be part of the scientific and methodological aspects of the protocol.
- 5.3. Section 3.5 (Informed Consent) of the protocol must clarify that participants will be informed of all the potential long-term risks of the IMPs and the requirement for long-term safety monitoring.

Answer:
5.1 We agree that long-term follow-up is important in establishing the safety of the IMPs into adult life and physical maturity. We note the scientific challenges that are associated with disentangling long-term effects of GnRHa and cross-sex hormones as most of those remaining on a trans-gender hormonal pathway will commence the latter post-16 years of age

while young people desisting will stop puberty suppressing hormones. We note that long-term effects of GnRHa as a single intervention in precocious puberty have been addressed via routine care follow-up and registries/observational cohorts. This has yielded acceptable safety knowledge (e.g., bone accrual trajectories, reproductive outcomes). The Sponsor, a University funded for this research by NIHR, cannot undertake a separate long-term follow-up without external funding. However, follow-up into adult life will occur through the NHS Register, which all young people attending the NHS Gender Services are asked to join. Please see section 15.5 of the updated protocol.

Young people and their parents/legal guardians entering the trial will be further asked to join the NHS Register at the time of assent/consent for the trial if they have not already done so and to re-consent if they have). The NHS Register will provide passively collected long-term data into adult life that includes long-term safety surveillance: opt-in registry linkage to NHS digital datasets (primary/secondary care, fracture codes, fertility-related procedures, mental health). The NHS Registry linkage into adult life is subject to legal changes which are under way, as many trans people change their NHS number and there is a need to create a legal pathway to match up the two numbers.

Within the 5.5 year initial funding period, Trial participants will be invited to complete annual follow up following the end of the main 24 month trial period, including questionnaires and DEXA scans. IRAS section B2, Trial PIS' and protocol tables 2, 4, and 5, and section 4.6 have been updated to reflect this.

5.2 We have withdrawn reference to funding.

5.3 The Trial PIS' have been amended to include information about potential longer-term risks and importance of consenting to the NHS Registry study.

6. There is currently no clear rationale for the proposed dosing strategy in the protocol. The sponsor should provide justification for the selected doses of the IMP (and any alternate IMPs), the planned treatment duration, and the timing of treatment exposure. This justification should specifically address the safety of the proposed regimen and explain why the selected doses and schedules are considered appropriate for the study population.

Answer: Section 5.2.3 of the protocol has been updated in answer to this point.

7. QT prolongation is a recognised risk with GnRHa. However, there is no provision in the schedule of assessments for systematic cardiac monitoring. Specifically, the protocol does not mandate the collection of 12- lead ECGs at any timepoint.

The protocol schedule of events must be amended to include 12 lead ECG at screening, baseline and every 6 months including the final visit at Month 24 for immediate GnRHa treatment arm and screening, baseline, every 6 months starting from month 12 including the final visit at Month 24 for the participants in delayed GnRHa treatment arm.

Answer: A universal 6-monthly ECG adds burden without clear incremental safety in this population. In precocious puberty, serial ECGs are not routinely required for GnRHa treatment; QT prolongation is not a paediatric safety signal for triptorelin in routine care. As per the response to GNA 4 and updated protocol tables 2,4,5 and section 4.14.2, ECGs will be administered at screening and where clinically indicated thereafter.

8. The protocol currently defines the screening period as “Day –XX to Day 0” but does not specify a maximum permitted duration. As a result, there is potential for variability and extended delays between consent and randomisation. This could lead to situations where participants enrolled at the upper end of the eligible age range (e.g. 15 years and 10 months) are exposed to unnecessary delays in treatment initiation and may reach adulthood during the trial without clarity on re-consent requirements.

The protocol must be amended to specify a defined maximum screening window (e.g. ≤ 8 weeks), within which all eligibility procedures and baseline assessments are to be completed.

Answer: We have addressed this point by amending Table 2, 4 and 5, and section 4.3 of the protocol.

9. The current protocol specifies assessment of quality of life (QoL) using the KIDSCREEN-10 questionnaire at baseline, Month 12, and Month 24 only. This frequency is inadequate. For all participants in PATHWAYS TRIAL (both arms) the schedule of events (table 5 & 6) must be amended so that the KIDSCREEN-10 is administered at least every 6 months (i.e. baseline, Months 6, 12, 18, and 24).

Answer: This request is agreeable and the protocol has been updated in table 2, 4 and 5. The Trial PIS has been updated to reflect this change.

10. The protocol currently specifies safety assessments based on a 6-monthly triptorelin regimen. However, alternate IMPs with 3-monthly or monthly dosing schedules may be used. In this scenario, the protocol does not ensure alignment of safety surveillance with each IMP administration.

The protocol must be amended to state that, if alternate IMPs with 3-monthly or monthly administration are used, a brief safety review will be conducted at each study medication administration visit. This review must include at a minimum:

a) Vital signs
b) Adverse event reporting
c) Concomitant medication review
d) Assessment of anxiety and depression symptoms (RCADS-25)
e) Assessment of suicidality and self-harm risk (ASQ)
f) Pregnancy test (POCBP only)

The sponsor is strongly advised to consider providing specific schedule of events for each alternate IMP.

Answer:
We agree that vital signs, adverse effects, concomitant medication and pregnancy tests should be obtained at every injection visit and have modified tables 2, 4 and 5 (Schedule of Events) and added section 4.16 (Injection Visit Safety Data Collection) to reflect this. Mental health measures (RCADS and ASQ) are measures of efficacy that would not be used for analyses if obtained at additional timepoints for some participants. Additional questionnaire completion risks participant fatigue and is disproportionate.

11. The protocol must be amended to clearly specify prohibited concomitant medications for the entire duration of participant involvement in the trial.

a. Medicinal products known to prolong the QT interval or associated with Torsade de pointes, including but not limited to class IA antiarrhythmics (e.g. quinidine, disopyramide), class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide), methadone, moxifloxacin, and antipsychotic agents.
b. Prolonged use of medicinal products associated with clinically relevant bone mineral density loss, such as systemic glucocorticoids (for >14 days) and traditional anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, valproic acid).
c. Use of puberty blockers outside this clinical trial.
d. Any other investigational medicinal products (IMPs).

In addition, the sponsor must provide clear guidance to the investigators on how to manage concomitant use of antidepressants (SSRIs, TCAs) if clinically indicated, as there is risk of QT prolongation

Answer: Section 5.7.2 of the protocol has been amended to include the aforementioned categories of prohibited concomitant medications. A clinical risk management algorithm has been added as an additional section (5.7.3) of the protocol.

12. The proposed discontinuation criteria are not acceptable in their current form. While the listed risks are clinically relevant, the current reliance on a general reference to "values >2.5 SD outside the mean" is insufficiently precise and open to inconsistent interpretation. Thus, the discontinuation criteria must be revised to add the following:

a. Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient, including serious or intolerable AE that prevents the subject from continuing with study participation
b. Change in compliance with any inclusion or exclusion criterion that is clinically relevant and affects subject safety, as determined by the Investigator.
c. Use of prohibited concomitant medications
d. QTc > 450ms
e. Pregnancy

Answer: This point has been addressed by adding the listed discontinuation criteria to section 5.6 (discontinuing allocated interventions)

13. In addition to participant-level discontinuation criteria, the following trial-level stopping rules must be applied to ensure adequate protection of this vulnerable paediatric population:

a. The occurrence of any serious adverse reaction (at least possibly related to IMP administration) in one subject.
b. The occurrence of two severe adverse reactions (at least possibly related to IMP administration), independent of whether they occur within the same or different system of organ classes. Also, the sponsor is required to include in the protocol that if the trial is halted due to safety concerns, or if the study stopping rules are triggered, the trial can only be re-started after regulatory authority approval via a substantial amendment.

Answer: Automatic full trial halt following a single SAR may lead to frequent, unnecessary stops for events that are serious by definition (e.g. hospitalisation for anxiety) yet not mechanistically

related. Further, HRA/MHRA frameworks already require expedited SAR reporting. Following discussion with the MHRA, the PATHWAYS team propose collection and reporting of data to the DMEC on the severity of non-serious adverse reactions where the causality is assessed as possible, likely or definitely. Protocol section 9.3 has been amended to reflect this proposal. Furthermore, section 14.3 now states the "DMC will assess adverse event data and can recommend a pause of enrolment and/or IMP dosing whilst it adjudicates relatedness and severity of safety events". We have subsequently amended paragraph 2 of protocol section 9 to clarify the KHP-CTO pharmacovigilance process.

14. The protocol does not provide an adequate plan for follow-up of participants who discontinue study treatment prematurely (for example, if they fulfil any of the discontinuation criteria per protocol). Simply encouraging participants to remain in the trial is not sufficient, particularly in cases where discontinuation is Investigator initiated for safety reasons.

The protocol must be amended to state that all discontinued participants remain in follow-up according to their randomised arm's schedule of events till the end of the study unless they explicitly withdraw consent.

Answer: Section 5.6 of the protocol has been amended to state the above.

15. The protocol section 9 must be amended as follows:

All Adverse Events and Serious Adverse events will be recorded from "the signing of the informed consent form" until 12 weeks following the final dose.

Answer: The first paragraph of protocol section 9 has been amended in response.

16. The schedule of events and section 4.14.2 states that tanner staging is optional for some of the study visits. This is not acceptable. The tanner staging assessment must be mandatory for participants in both treatment arms, performed by a qualified, adequately experienced physician at visits specified in the schedule of events. The protocol must be amended to make this clear.

Answer: Tanner stage is not an outcome or safety measure in this study. Mandating Tanner staging at every visit introduces unnecessary invasiveness, especially for adolescents with gender dysphoria, and risks psychological harm, which conflicts with the principle of minimising risk and discomfort.

HRA guidance on research with vulnerable populations emphasises respect for dignity and privacy. Repeated genital examinations can be perceived as intrusive and may increase withdrawal rates, undermining trial integrity.

In Precocious puberty trials and NHS practice, Tanner staging is not performed at every visit once diagnosis and baseline staging are established. Pubertal progression can be reliably tracked without repeated mandatory physical staging, especially when combined with biochemical markers.

The primary endpoints (psychological outcomes, QoL, safety labs) do not require Tanner staging at every timepoint.

17. The current protocol (Section 4.15.1.1, follow up visits) specifies that only FSH, LH, Oestradiol, Testosterone, and Liver Profile are required at each visit, with Full Blood Count, Prolactin, Renal, Lipid, and Bone Profiles performed only if clinically indicated at

investigator discretion. This approach is inadequate for ensuring consistent and systematic safety monitoring across all participants.

The protocol must be amended to add the following mandatory laboratory tests at all follow-ups visits:

a) Full Blood Count
b) Prolactin
c) Renal Profile
d) Lipid Profile
e) Bone Profile
f) Magnesium

Answer: We agree to add all these investigations as mandatory at 6 monthly follow-up visits. Section 4.15.1.1 has been amended appropriately.

18. There is a possibility that the participants randomised to delayed arm may access puberty blocker therapy outside this clinical trial. The protocol must include details on how such use will be monitored along with clear guidance for the investigators on how to manage such cases.

Answer: Research exclusion criterion 1 has been amended to make this clearer.

19. Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in paediatric patients receiving the IMP. The protocol must be amended to state that participants should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, vision disturbances and tinnitus.

Answer: Section 8.3 of the protocol has been amended to include wording around warning participants of signs and symptoms of suspected idiopathic intracranial hypertension.

Part 2: REC Queries

1. Please provide additional information around the current and previous standard of care treatments for this group of patients as well as what potential future standard of care may look like if the results of this application reveal that puberty blockers are not beneficial.

Answer:
Previous UK practice: psychosocial care as first line; puberty suppression with GnRHa available initially under research study (until 2014, non-randomised), then adopted in routine care at the Tavistock GIDS for selected cases.

Current UK practice (from 2024): NHS England does not routinely commission GnRHa for gender incongruence/dysphoria in under-18s. Cross-sex hormones can be considered for those older than age 16. Private supply and dispensing routes have been restricted by government, with an indefinite ban on sale/supply for this indication to under-18s outside NHS-led pathways; ongoing NHS reforms are implementing the Cass Review.

If PATHWAYS shows no benefit / net harm of GnRHa: likely future standard would continue to exclude routine NHS use, with focus on holistic, multidisciplinary psychosocial care within the CYPGS service model being rolled out; puberty blockers would remain restricted to research or be decommissioned for this indication pending new evidence. Conversely, if benefit/risk is

favourable, NHS England has signalled access would be through an ongoing research programme leading to possible commissioning decisions.

2. Provide additional information around the potential treatment options that will be made available to participants at the end of the study. This should include who will decide whether puberty blockers will continue to be available and how continued access will be possible given the current restrictions around access. The potential options should also be clear in the information sheets.

Answer:
The Protocol states the post-trial "Continuing care" approach in section 4.7: continuation only if (i) covered by routine NHS commissioning or (ii) via a commissioning statement specific to PATHWAYS participants; requires ongoing CYPGS oversight, NMDT recommendation, shared decision-making, and a confirmed NHS prescriber. We have lifted this into a prominent box and reproduced it in all relevant PIS versions.

We have made explicit that decisions are made by: the CYP/parent(s)/legal guardian, the CYPGS lead clinician, and the National MDT (NMDT), within the commissioning framework for each UK nation. The practical route under present restrictions is via NHS-led continuation if a nation-specific commissioning statement permits it and the NMDT recommends it; otherwise, GnRHa cannot be continued.

3. Provide additional information around the long term follow up plan and how likely it will be to secure funding to support this as the Committee feel that this is a vital aspect of the study.

Answer:
PATHWAYS is funded for 5.5 years with annual follow-up of all (both TRIAL and HORIZON Intensive participants) for the duration of funding. All PATHWAYS participants are asked to assent/consent to longer-term follow-up through NHS data linkage, which will include safety and wider outcome data into adult life (e.g., bone accrual trajectories, reproductive outcomes safety surveillance) and opt-in registry linkage to NHS digital datasets (primary/secondary care, fracture codes, fertility-related procedures, mental health). The NHS Registry linkage into adult life is subject to legal changes which are under way, as many trans people change their NHS number.

We will consider NIHR grant application in Y3 or MRC/UKRI cohort extension. We will use of routine data linkages (HES, mental health services data, imaging repositories). NHSE/NIHR also have expectations that longer-term safety and effectiveness evidence for these interventions merits priority.

4. Please make the following changes to the protocol:

a. Create a clear process relating to serious adverse events including how and when they should be referred to the DMEC and regulatory authorities as per the HRA website Safety and progress reports (CTIMPs) procedural table - Health Research Authority.
b. State that part of the urine sample test is to monitor a participant's glucose level as diabetes is a potential side effect of the medication.

Answer: As aforementioned in GNA 13 above the protocol (section 9) states the reporting requirements and timelines for SAEs, SARs, and SUSARs, outlining the broad safety related content of DMEC reports. Point 4b has been answered in an amendment to the wording in protocol section 4.15.3 (urinalysis).

Part 3: TOXICOLOGY – Non Clinical Grounds for Non-Acceptance

1. For Zoladex, no information on genotoxicity is provided in the SmPC. The Sponsor must discuss the potential for genotoxicity in the intended patient population. Supportive information may be available from safety data sheets or the US label/prescribing information

2. For Zoladex, the SmPC states 'Zoladex LA is not indicated for use in children, as safety and efficacy have not been established in this patient group'. To include this medicinal product as an alternative regimen, the Sponsor must provide a scientific justification to support the administration of Zoladex in the proposed patient population which includes children. This justification must include a discussion of safety and efficacy, using all available non-clinical and clinical data, relevant to the proposed patient population.

   In addition, no information on posology for children is included in the SmPC for Zoladex. Therefore, the Sponsor must provide a scientific justification to support the proposed clinical dose of Zoladex in children. Alternatively, in the absence of supportive information, this treatment option must be removed from use in the trial.

Answer: In answer to points 1 and 2 and following discussion with the MHRA, Zoladex has been removed as an IMP from the PATHWAYS Trial protocol and application. Zoladex LA (Goserelin) was previously included in protocol sections 5.2.3, 8.6, and appendices C & D. In accordance with this amendment, section 9.1 (reference safety information) has been updated to state the SmPC for each GnRHa preparation, specifically the 'general tolerance in children' tables, are to be referred to for assessment of expectedness.

3. An amended protocol (complete, signed document) must be submitted to address the following (a commitment to submit an amended protocol before dosing the first trial participant will not be acceptable):

   The SmPCs for the investigational medicinal products state that non-hormonal methods of contraception should be employed during treatment until menses return. The list of effective methods of contraception for use in the trial must be updated to remove all hormonal methods of contraception. The duration of contraception, which is currently stated as 'at least three months after stopping GnRHa' must be updated, according to the requirements of the SmPCs, i.e. until menses return.

Answer: The list of effective methods of contraception in section 3.2.1.3 have been updated alongside the accompanying wording.

Part 4 – GNA Remarks: REC Queries

1. Provide additional information around the specialist team that will be discussing potential fertility options with potential participants and what experience they have of such a sensitive area with a vulnerable population. Also state what potential options, such as sperm donation and egg retrieval, will be given and how long they will be given to decide whether to take any of these options. This information should also be clear in the information sheets.

Answer:
Section 3.5.1 has been expanded and now reads:
Fertility: The risks to long-term fertility will be discussed with each CYP considering GnRHa by a clinician in or attached to their Gender Service who has specific training and knowledge

about fertility risks and options available to them as well as training in working with CYP experiencing gender incongruence. The information will include options around sperm donation and egg retrieval. CYP will be encouraged to ask questions and explore fertility preservation options prior to commencing on GnRHa (if found clinically and research eligible). For those wishing to pursue fertility options at this time, a referral to specialist fertility preservation services will be facilitated by the Gender Service, noting that referrals are made either directly by paediatric endocrinologists or by the CYP's GP. There will be no upper limit imposed by research consent on how long young people have to consider and then explore fertility preservation options, and potential participants will be reminded of other constraints, e.g., around the upper age limit of the study.

Further information is included in section 6 of the PIS for young people and their parents/legal guardians.

2. The Committee feel that providing vouchers to participants might be considered a financial inducement to participate. Please remove this aspect in the protocol and information sheets.

Answer:
This advice was clarified with the REC Chair to relate only to CYP in the Trial and for completion of questionnaires that relate to Trial outcomes (not to HORIZON Intensive participants or to the optional brain imaging study, CONNECT). The protocol and Trial PIS have been modified to remove payment for CYP (and parents/caregivers) for completion of questionnaires in the Trial.

3. State how it will be ensured that participants completing questionnaires in conjunction with a translator will be appropriately supported due to the sensitive nature of the questionnaires.

Answer: Professional NHS interpreters only will be used with support from researchers. Interpreters adhere to confidentiality, impartiality, and safeguarding standards. Sensitive self-report items (e.g., ASQ, APCTSS, SCOFF) will be self-completed in ePRO with privacy; the interpreter may explain instructions.

4. Provide a rationale for the proposed blinding status of researchers as per section 6.3 of the protocol, including why the trial statistician will be initially blinded to complete the Statistical Analysis Plan and then unblinded to complete DMC reports.

Answer: The blinding of researchers is in adherence to the KCL Department of Biostatistics & Health Informatics Standard Operating Procedures and recommended best practice.

Statistician blinding plan: The SAP is drafted before any accumulating data is reviewed. The Senior Statistician remains blinded to treatment allocation until the Statistical Analysis Plan (SAP) is signed-off, to avoid analytic bias; the Trial Statistician is unblinded thereafter solely to prepare closed DMC reports.

5. The Committee was not assured that the current contraceptives proposal is suitable, but recognised that this would form part of the MHRA's review. Any request for action and/or information in this area which comes from the MHRA should be reflected in the protocol and all information sheets.

Answer: Please refer to the answer provided In Part 3 GNA 3

6. Make expenses available not only to patient participants but also parents/guardians. Update the protocol and information sheets to reflect this.

Answer: Protocol section 4.18 has been amended to clarify expenses are available to parents/guardians - all relevant PIS' have been updated to reflect this.

7. Please make the following changes to all information sheets:

a. Use only PATHWAYS and not its full definition so as not to imply that this study relates to transitioning.
b. Create a specific section titled 'Risks or possible risks of taking part in the study' and detail all potential risks as well as any mitigations taken by the research team and how a participant should react if they experience any side effects. This includes clearly relaying the potential impacts of the study drug on cognitive abilities, bone density and fertility.
c. Include the potential risks of MRI scans, including claustrophobia, and what steps the research team take to mitigate these.
d. Ensure that the frequency of injections given from the outset of treatment is clear.
e. State how a participant would go about withdrawing from the study if they chose to do so.
f. Some information sheets state that if scans reveal abnormalities then parents will be informed. This should be stated in all information sheets.
g. Explicitly state what will happen at the end of the study and the potential likelihoods. If it is not possible to know what will happen, this should be stated clearly.
h. Rephrase reference to the data monitoring and ethics committee to make it clear that this is not affiliated with the Research Ethics Committee that reviewed the study.
i. Any potential impacts on school attendance by participating in the study should be made clear.
j. The information sheets are inconsistent in terms of doctor, clinician and researcher. For instance, one flowchart refers to questionnaires being delivered by a doctor whereas another states it will be delivered by a researcher. Please review and ensure consistency.

Answer: All requested changes have been made to the participant information sheets. Regarding point 7j, 'clinician' has been replaced with 'doctor' for consistency, however the flowchart accurately reflects the schedule of events. For example, delayed arm participants will be contacted by a researcher prior to starting treatment at 12 months, whereas immediate arm participants will be contacted by a doctor.

8. Please make the following changes to the under 16 assent form:
a. Include a clause relating stating outright that they understand the potential impacts of puberty blockers, i.e. potential reduction in bone density, potential fertility impacts and potential cognitive impacts.
b. Add a short explanation of the phrase 'chaperone'.

Answer: Clause 9 has been added to the under 16 assent form to address point 8a. An explanation of the word 'chaperone' has been added to clause 7.

9. Please make the following change to the APCTSS Parent document:

a. a. Replace ‘mad’ with ‘angry’ in question 4.

Answer: The PATHWAYS team acknowledge the rationale for this request, however it is felt that replacing the language of a validated measure is inappropriate scientifically.

10. Please make the following changes to the BISGS Body image screen:

a. The directions state that answers should be ‘checked’. Replace with ‘ticked’.
b. Question 33 refers to stature. Please add a short explanation of this phrase in brackets.

Answer: The applicant has been in correspondence with the REC regarding this request in relation to PATHWAYS HORIZON (IRAS 350909). In agreement with the authors of the measure, the BIS-GS has been amended to replace ‘check’ with ‘tick’ and stature has been explained as “(figure/body shape)”. The updated measure is provided in the response documents.

11. Please make the following changes to the SCOFF for parents:

a. Add a metric equivalent to stones and pounds.
b. Change “ ‘you’ are too thin “ to “ ’you are too thin’ “.

Answer: A metric equivalent to stones and pounds will be programmed into the ePRO system under the question, in line with the PATHWAYS HORIZON (IRAS 350909) database, reading “Note: One stone is approximately 6kg or 14lb”. An incorrect SCOFF parent version was provided in the initial submission documents in error. The correct version is v1.1 28.05.25 in alignment with PATHWAYS HORIZON and is provided in the response documents.

12. Please make the following change to the Scoff for young people:

a. Add a metric equivalent to stones and pounds.

Answer: Please see answer to 11 a above

Note Only

1. Please note that any additional recruitment materials, including documents designed to support participant understanding of the recruitment process, need to be submitted for review by the Committee either as part of a response or via an amendment.

Answer: IRAS Ethics Question Set section H2 (what resources will be used for recruitment) has been amended to remove mention of providing in-depth information such as diagrams, charts, checklists etc., as well as leaflets and posters to be displayed in CYPGS waiting areas. This approach is no longer accurate.

REC Assessment Queries

1. Please adopt the HRA's recommended transparency wording in all information sheets verbatim with no additional wording. The wording can be found at: GDPR transparency wording for all sponsors – Health Research Authority

Answer: All information sheets have been amended to adopt the HRA’s recommended transparency wording.

2. Please remove reference to REC having access to participant data from all information sheets as this is not correct.

Answer: The PATHWAYS Team have reviewed all participant information sheets and cannot find reference to the REC having access to participant data. The updated PIS' now refer to the "DMC" as opposed to "DMEC" and clarify they are a separate body to the REC.

3. Please review section 1.2.1 figure 1 in the protocol as it currently refers to 2000-2017 however the actual figure shows 2009-2021.

Answer: Section 1.2.1 referencing figure 1 has been updated to reflect the correct time period.

4. Please provide a copy of the insurance policy and confirm that there no exclusions related to minors

Answer: The KCL insurance policy for 2025-26 was included within the original submission documentation. Please see documents entitled 'No Fault Compensation for Human Clinical Trials TWIMC 2025-2026', 'Legal Liability for Human Clinical Trials TWIMC 2025-2026'. There are no exclusions for minors, however the policy states a trial involving any subject who is under the age of 5 years at the time of participation would need to be referred to the insurers for review.

5. The IRAS form states 'Only after a CYP has been confirmed as clinically eligible for GnRHa will they be referred to the PATHWAYS research team. At this point, the research team will be provided with limited identifiable information (e.g. name, date of birth, contact details) solely for the purpose of discussing potential participation in the study' Please confirm that the identifiable data will only be passed to the research team with the consent of the individual.

Answer: As per protocol section 3.5.1.2, CYP deemed clinically eligible for GnRHa and providing verbal consent to be contacted will be contacted by the research team, who will confirm the nMDT checklist was fully completed prior to the nMDT review outcome.

Please note, all participant information sheets have been updated to version 1.1 08.10.25 to include the REC reference number on the header.

The following documentation has been updated as part of the response. Tracked and clean versions are included:

- PATHWAYS Trial Protocol V2.0 29.09.2025
- PATHWAYS Trial CYP & Parent PIS V1.1 08.10.2025
- PATHWAYS HORIZON INTENSIVE CYP & Parent PIS V1.1 08.10.2025
- PATHWAYS CONNECT (TRIAL) CYP & Parent PIS V1.1 08.10.2025
- PATHWAYS CONNECT (HORIZON INTENSIVE) CYP & Parent PIS V1.1 08.10.2025
- CONNECT CYP 16+ Consent Form V1.1 08.10.2025
- CONNECT CYP u16 Assent Form V1.1 08.10.2025
- CONNECT Parent u16 Consent Form V1.1 08.10.2025
- HORIZON Intensive CYP 16+ Consent Form V1.1 08.10.2025
- HORIZON Intensive CYP u16 Consent Form V1.1 08.10.2025
- HORIZON Intensive Parent u16 Consent Form V1.1 08.10.2025
- TRIAL CYP u16 Assent Form V1.1 08.10.2025
- TRIAL CYP 16+ Consent Form V1.1 08.10.2025
- TRIAL Parent u16 Consent Form V1.1 08.10.2025

- BIS-GS CYP V1.1 11.09.25
- SCOFF Parent Caregiver V1.1 28.05.25

Please do not hesitate to contact us if you require further information or clarification on any of these points.

Yours faithfully,

[redacted]

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