FAQs FOR PATHWAYS TRIAL and

PATHWAYS CONNECT INCLUDING HORIZON INTENSIVE COHORT

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Purpose of the Document

The aim of these FAQs is to provide easily accessible information about two parts of the PATHWAYS study that have been approved — PATHWAYS TRIAL and PATHWAYS CONNECT. This includes information about the HORIZON INTENSIVE cohort, who are part of PATHWAYS CONNECT. They also explain why the studies are being done and what they will involve. If you are interested in finding out more about other parts of the PATHWAYS study, you can go to the PATHWAYS Study website.

1 Background

1.1 What is gender incongruence?

Gender incongruence is when a person's gender identity does not match their sex registered at birth. It often involves a strong dislike of the person's sexual anatomy, a feeling which may become stronger and more distressing during puberty. The clinical diagnosis is made according to the World Health Organization's diagnostic manual, the ICD-11, with strict criteria including persistence of gender incongruence for at least two years. In recent years we have seen a very large increase in the number of young people experiencing gender incongruence, and we don't know why, or fully understand their needs.

The NHS Children and Young People's Gender Service has been set up to provide specialist care for young people with gender incongruence, offering a range of different treatments including psychological and social support and physical health interventions, for children and young people[1]. However, there is not enough research to understand the outcomes of these different types of treatment, and who may benefit from them, as highlighted in the Cass Review[2].

1.2 What is the PATHWAYS Study?

PATHWAYS is a group of inter-related studies looking at the care needs and treatment of children and young people attending NHS specialist gender services.

NHS England accepted the Cass Review recommendation to build a more robust evidence base through a carefully considered research programme. The PATHWAYS Study, funded by the National Research Collaboration Programme (NRCP), an NHS England and National Institute for Health and Care Research (NIHR) partnership, is part of that plan.

By exploring the needs and treatment of children and young people attending the NHS specialist Gender Service, the PATHWAYS Study will provide important information about these different treatment options, to help young people with gender incongruence, their

[1] In the document, 'children' generally refers to those under age 12 years while 'young people' refer to those 12-18 years, as a general (but not fixed) guide.

[2] Cass H. The Cass Review: Independent review of gender identity services for children and young people: Final report.; 2024.

families and health professionals to make more informed choices about the care and support options that are most likely to be helpful.

PATHWAYS consists of several studies. All parts of the study have been designed to meet rigorous scientific and ethical standards.

PATHWAYS HORIZON is an observational study of all children and young people attending the NHS Children and Young People's Specialist Gender Services. It aims to understand how their quality of life, mental and physical health and gender identity develop over time and how these are related to care received in the Gender Service.

HORIZON participants, including their parents/caregivers, will be asked to complete questionnaire measures about their experiences, mental health, and quality of life on an annual basis throughout the course of the study. The study will last for the duration of the funding period (5.5 years). All children and young people attending the NHS Children and Young People's Gender Service will have the opportunity to participate in HORIZON.

PATHWAYS TRIAL is a randomised controlled trial of the effects of puberty suppressing hormones on young people's physical and mental health, their thinking and learning, their wellbeing and gender identity. As explained below, only a very small number of the young people attending the Gender Service are expected to be suitable for this intervention and trial.

PATHWAYS CONNECT is a brain imaging study that looks at brain development in young people attending the NHS Children and Young People's Gender Service. It compares those who are receiving puberty suppressing hormones with those who are not. It will see how brain development links to young people's thinking and learning.

PATHWAYS TRIAL and PATHWAYS CONNECT have now received ethical and regulatory approval, and the research team are working closely with the NHS Children and Young People's Gender Service to support the start-up of these two PATHWAYS Studies.

PATHWAYS VOICES will interview young people and their parents/caregivers about their experiences of living with gender incongruence and of their care in the Gender Service.

All PATHWAYS studies are informed by two independent lived experience advisory boards of young adults and parents [are they parents or carers/guardians?], convened by the National Children's Bureau.

1.3 Why are PATHWAYS TRIAL and CONNECT needed?

Many different interventions are used to help young people with gender incongruence, including psychological support, voice training and medical management of related issues, such as periods. Puberty suppressing hormones have also been used in some cases in order to stop further development of puberty. The Cass Review looked at puberty suppressing hormones and concluded that existing evidence regarding both the possible benefits and also risks of puberty suppressing hormones is inconclusive.

Puberty suppression is used to allow young people with gender incongruence to explore their gender identity without worrying about their bodies developing further changes. It is thought the treatment might reduce anxiety and distress and therefore allow them to focus more on relationships with their family and friends, leisure activities and

education. However, the studies that have examined this are inconsistent in whether they find these benefits. Because the young people in the studies may have received other treatments at the same time, it isn't possible to know whether any benefits are due to receiving puberty suppressing hormones.

We also don't know enough about the safety and possible risks for young people taking puberty suppressing hormones. Puberty suppressing hormones have been used for many years for precocious puberty (when puberty occurs at a very early age) and they are safe and well-tolerated in the short term in this context.

However, there is less knowledge about their safety when used for gender incongruence, particularly regarding longer-term possible adverse effects. Puberty suppressing hormones can affect bone strength and it is not certain whether this completely recovers when the treatment is stopped or young people go on to receive other interventions such as cross-sex hormones. Because puberty is a time of rapid brain and cognitive (thinking) development, it's been argued that puberty suppression might adversely impact these, but they have not been properly studied.

The Cass Review emphasised the need for rigorous, long-term research to better understand the treatment's safety and effectiveness. As a result, the UK Parliament passed a law banning the use of puberty suppressing hormones outside of a research study, meaning that doctors in the UK are now not able to give this treatment to young people with gender incongruence unless it is part of a research study.

2 PATHWAYS TRIAL

2.1 How will PATHWAYS TRIAL study puberty suppressing hormones?

PATHWAYS TRIAL will use a randomised controlled trial design, as this method can determine whether puberty suppressing hormones cause benefits and/or risks. This approach helps ensure that any observed effects can be attributed to the specific treatment itself, rather than other parts of care that patients may have received.

The trial will compare impacts on young people's physical, social and emotional wellbeing and cognition between two groups: one being offered puberty suppressing hormones immediately and the other after one year. This will help us understand whether earlier intervention improves quality of life, mental health, or reduces distress, and what are the effects of longer versus shorter length of treatment.

2.2 Who can take part in PATHWAYS TRIAL?

The trial will only include young people who want this treatment, have consent from their parents/legal guardians and are deemed clinically eligible by their care team and the National Multidisciplinary Team (NMDT). It is expected this will be a very small group of the young people attending the Gender Service. If young people and their parents/legal guardians agree to participate in PATHWAYS TRIAL, they will be randomised (allocated by chance) to be offered puberty suppressing hormones immediately, or after a delay of one year. They will have an equal chance of being offered puberty suppressing hormones immediately or after one year.

To be included in PATHWAYS TRIAL, a young person's clinical eligibility will be considered both by their NHS clinical care team and by the NMDT. The NMDT is a group of senior clinicians from the NHS Children and Young People's Specialist Gender Service who ensure that decisions about eligibility are made consistently across clinicians and services. The team reviews information about each young person's psychosocial and physical health, education, and safeguarding to make sure assessments consider all aspects of a young person's presentation. Young people will need to meet clinical criteria for a diagnosis of gender incongruence according to ICD-11 and have received appropriate care for any other conditions or experiences that might be affecting their gender incongruence.

The young person's clinical care team will assess the individual's NHS clinical eligibility for PATHWAYS TRIAL. This will happen after they have had a comprehensive assessment and been offered any other interventions that are appropriate for them. In most cases, these other interventions may last for up to a year and might also continue after starting in the trial.

The potential participant will receive detailed information about the benefits and possible risks of puberty suppressing hormones, including information regarding fertility preservation. The young person and their parents/legal guardians must be able to show that they fully understand the possible benefits, risks, and long-term effects of treatment. This understanding is developed through a series of detailed discussions with clinical specialists in the gender service and those who have expertise in hormonal interventions.

Over and above the rigorous assessment of clinical eligibility, young people need to agree to take part in the trial and not have received puberty suppressing or cross-sex hormones for gender incongruence

2.3 How will young people receive puberty suppressing hormones?

Puberty suppressing hormones are given by injection. The most common drug used is called triptorelin and it is usually given every six months. It can also be given more frequently but in a smaller dose, and there are other drugs that can be used, if a young person experiences side effects.

Young people and their parents/legal guardians will be told whether they are starting treatment immediately or after a one-year delay. Those in the delayed treatment group will start receiving injections only after one year.

2.4 How will the research monitor the safety of participants during the study?

Before entering the study, doctors will ensure there are no health reasons why this treatment should not be used. The young person will have X-rays for bone health, blood and urine tests, vital signs, and an electrocardiogram (ECG). A physical examination will also check young people's health and will determine what stage of puberty they are at (Tanner staging).

Young people taking part in PATHWAYS TRIAL will have medical tests and scans, including height and weight measurements, blood and urine tests, bone scans and cognitive assessments to monitor their growth, health and development every six months to one

year during the study to check the treatment is still low risk. The young people will be asked to complete regular questionnaires so that we can monitor their wellbeing and understand how they're feeling.

All young people will also have regular check-ins with their care team at the NHS Children and Young People's Gender Service. Participants will be advised to speak with the doctor who is providing their puberty suppressing hormones as soon as they notice any symptoms or side effects of the treatment.

2.5 What are the potential side effects of puberty suppressing hormones?

Puberty suppressing hormones have been licenced for use in children experiencing precocious (early) puberty since 1986, where they are generally well-tolerated and have a good safety profile. However, precocious puberty is a condition where puberty occurs abnormally early, and the aim is to slow it down. In contrast, in gender incongruence, the aim is to suppress normal puberty. This may lead to a different balance between benefits and risks. These will be carefully monitored in PATHWAYS TRIAL.

2.5.1 Short-term side effects

Most side effects when taking the treatment are mild and go away when treatment stops. Common short-term effects include headaches, hot flushes, tiredness, mood changes, and soreness where the injection is given. Some people may feel more anxious or low in mood.

There are also some less common but important risks. These medicines may affect bone health by slowing down bone strength development. We do not know whether this persists after stopping puberty suppressing hormones. Very rarely, a condition called idiopathic intracranial hypertension can occur, which causes severe headaches, vision problems, or ringing in the ears. There is a very small chance of changes in heart rhythm, especially if puberty suppressing hormones are taken alongside other medicines. The study will carefully monitor for common and more rare adverse effects.

2.5.2 Longer-term possible effects

Some possible risks may not show up until later in life. These include possible effects on:

- Future fertility, especially if young people go on to cross sex hormones like testosterone or oestrogen
- Bone health – increased risk of fractures
- Sexual development and function
- Memory and thinking skills

There currently isn't any evidence about how common these are or whether these effects are directly related to puberty suppressing hormones. This is because studies that exist look at people who choose further treatments such as cross-sex hormones. This means these effects have not yet been comprehensively studied for puberty suppressing hormones on their own.

2.6 What is the age range of the young people expected to take part in PATHWAYS TRIAL?

Because the study drug acts by suppressing or delaying puberty, eligibility for PATHWAYS TRIAL is determined by a person's stage of pubertal development, not their chronological age. Puberty timing can vary greatly between individuals, so age alone is not a reliable indicator of biological maturity.

We use a recognised medical scale called the Tanner scale, which describes the physical stages of puberty. Participants can take part from Tanner stage 2, marking the onset of puberty, up to Tanner stage 5, representing near full physical maturation.

The upper age limit at consent is 15 years 11 months. This ensures participants enter the study during mid-puberty, allowing enough time to observe treatment effects before full maturation. This also aligns with NHS commissioning guidance and ethical safeguards for paediatric research, ensuring the intervention remains clinically relevant.

Over and above being in puberty, young people will need to meet all the other eligibility criteria, which include demonstrating a good understanding of the intervention and its possible benefits and risks. Ethical practice dictates that children who are clinically eligible should not be discriminated against on age alone. Nevertheless, it is very unlikely that many of those under age 11 years will show the necessary level of understanding of the treatment to be able to take part.

2.7 What information will young people and their parents receive to decide whether to take part?

Everyone considering participation will receive a Participant Information Sheet with details about PATHWAYS TRIAL and information about the puberty suppressing treatment being investigated. Information can be provided in written and alternative formats (visual) material and audio-recordings adapted to meet individual needs. NHS interpreter services will be available for those who are not confident in their use of English.

Before deciding whether to take part, each young person will have a series of meetings with clinicians, both individually and together with their parent(s) or legal guardian(s). These meetings will cover the known and unknown possible benefits and risks of puberty-suppressing treatment, potential long-term effects and alternative treatment options. Doctors will discuss fertility, including possible long-term effects and options for fertility preservation such as sperm or egg storage. Young people will have the option to see a fertility specialist.

Clinicians will check understanding by asking the young person and their parent(s) or legal guardian (s) to explain the information in their own words or preferred communication method. If there is more than one parent or legal guardian, both will be invited to share their views independently, and any differences will be reviewed by the multidisciplinary team overseeing the study.

Potential participants will be encouraged to speak with their clinical care team or to contact the research team should they have any further questions. The research team will only be in touch with young people and their families after it has been determined that they are clinically eligible.

Young people and their parents/legal guardians can take as much time as they want to make up their minds about joining PATHWAYS TRIAL.

2. 8 Who needs to give consent to PATHWAYS TRIAL?

PATHWAYS TRIAL requires consent from a parent/legal guardian for a young person to participate. Young people under the age of 16 years are legally not able to provide fully informed consent for research on their own. In PATHWAYS TRIAL, we will also get young people's agreement to participate, called assent. This is the standard practice for all research studies involving young people under 16 years.

2.9 What support will young people get if they decide not to take part in PATHWAYS TRIAL?

Young people will be fully supported whatever they decide about taking part in PATHWAYS TRIAL. As mentioned above, they and their parents/legal guardians can take as much time as they need to make their decision.

If a young person decides not to take part in PATHWAYS TRIAL, their routine care in the Gender Service or anywhere else in the NHS will not change. They will be able to discuss other treatment choices with their care team at the NHS Children and Young People's Gender Service, for example, psychological therapies or non-endocrine pharmacological treatments (treatments which do not primarily affect hormone production).

If a young person decides not to take part in PATHWAYS TRIAL, they will still be eligible to take part in PATHWAYS HORIZON.

2.10 Can a young person leave the trial and stop taking puberty suppressing hormones if they want to?

Anyone taking part can decide to stop taking puberty suppressing hormones and leave PATHWAYS TRIAL at any time. They do not need to give a reason. If they decide to stop taking part in PATHWAYS TRIAL, we will ask if it is ok to continue collecting study-specific information about their health to help make the study results useful for others.

If a young person decides to stop taking puberty suppressing hormones, their care in the NHS Children and Young People's Gender Service or anywhere else in the NHS will not change in any other way, and their doctors will talk to them and their parents/legalguardians about the treatment options available to them.

If a young person decides to stop taking part in PATHWAYS TRIAL, they will still be eligible to take part in PATHWAYS HORIZON.

2.11 How long will the researchers follow participants for?

Participants taking part in PATHWAYS TRIAL will be regularly followed up in the trial for 2 years after their baseline assessment. During this time, they will complete research procedures every 3 months.

After the first 2 years, all participants will be included in annual follow-up throughout the study period. Follow-up into adult life is important and participants will also be asked to consent to long-term follow-up through ongoing involvement with the PATHWAYS team, with a national health registry for gender care and linkage to health information routinely collected by NHS England.

2.12 What will happen when a young person comes to the end of their two years of treatment within PATHWAYS TRIAL?

When the trial ends, the young person's doctor will talk to them and their parents/legal guardians about how they have found the treatment in terms of their quality of life, mental and physical health and their experience of their gender and body. Young people will discuss the next steps for their care, what the options are, and what they would like to do. These might include staying on puberty suppressing hormones, stopping the treatment, or going on to another treatment.

It is not possible to know before starting puberty suppressing hormones what the treatment plan for any single young person will be at the end of the trial. This will depend on several factors, including their experience of puberty suppressing hormones, their mental and physical health, and their preferences for future care. We also do not know whether safety monitoring from the trial more generally may be showing that there are significant risks from this treatment, which could mean it is not a good idea to stay on puberty suppressing hormones.

If a young person wants to stay on puberty suppressing hormones and their doctor in the NHS Children and Young People's Gender Service agrees that they may continue to benefit from it, their care will be reviewed again by the NMDT, who will need to agree that they should stay on puberty suppressing hormones. If the NMDT don't agree, they will give the young person reasons why they think this is not the right ongoing care for them. If they make that decision and the young person's circumstances change so the reasons they gave no longer apply, the young person's doctor can ask for another review of your care.

If a young person stays on puberty suppressing hormones their care will need to be reviewed by the NMDT every year while they are on it, to check it is still the right treatment for them.

2.13 How many young people are expected to take part in PATHWAYS TRIAL?

The study expects to include 226 young people. Every child and young person who meets the clinical eligibility criteria and is approved by the NMDT will be able to enter the study, provided there are no health or other safety concerns. We don't know exactly how many young people will want puberty suppressing hormones and how many of these will meet the rigorous clinical eligibility criteria. The study has estimated it will be around 226 young people who enter PATHWAYS TRIAL. With this number of participants, we can detect a moderately large difference (benefit or harm) between the two treatment groups.

Recruitment will continue across all participating NHS sites for three and a half years, and the design allows valid conclusions even if the final number is slightly lower.

This approach ensures the trial is as inclusive as possible while maintaining scientific rigour.

3 Is PATHWAYS TRIAL the right study?

3.1 What is the ethical basis for PATHWAYS TRIAL?

Randomised controlled trials are undertaken when there is uncertainty about the effectiveness and/or the safety of an intervention. This is called equipoise and means that there is a roughly equal chance of either outcome – in this case whether the treatment is helpful overall or it is not helpful overall, when balancing any benefits and there is a reasonable chance that a randomised controlled trial will help find that it is helpful overall or unhelpful overall.

We described above (Section 1.3) how the evidence for either benefits or risks of puberty suppressing hormones is very uncertain. This means that we are at clinical equipoise for puberty suppressing hormones and there is a reasonable chance that a randomised controlled trial will find that it is overall helpful or overall unhelpful.

There are also questions about the balance of longer-term effects between those that are helpful (for example better psychological adjustment, better alignment of body shape with gender) and those that are harmful (bone health, possible effects on brain development and sexual health). These are important questions, but we don't know the answers yet. We first need to examine short-term effects and then follow young people up into adult life. This is why PATHWAYS TRIAL is so important.

3.2 How does PATHWAYS TRIAL ensure fair access to puberty suppressing hormones?

The study is designed to closely reflect standard NHS care practices, with the same clinical safeguards and oversight. All participants must meet strict eligibility criteria, including having had gender incongruence for at least two years, undergoing a comprehensive assessment by the NHS Children and Young People's Specialist Gender Service, and having participated sufficiently in other forms of care for gender incongruence.

All young people and their families will receive comprehensive information about the available evidence and will be given the time and support they need to make a decision about whether research participation is right for them.

This means that PATHWAYS TRIAL can be accessed by the same group of young people who would receive the treatment if it were subsequently made available as part of NHS care.

3.3 Why does PATHWAYS TRIAL compare immediate and delayed offer of puberty suppressing hormones?

PATHWAYS TRIAL will use a randomised controlled trial design in which an immediate start group is compared to a delayed start (12-months) group. This design will be used to

estimate the short-term effects of treatment at 12 months by comparing the difference between the two groups as well as the cumulative effect of treatment at 24 months.

Scientists use different study designs depending on the question they are asking. Many people are most familiar with 'placebo-controlled, double-blind' trials. A placebo-controlled study is when some people taking part receive the real treatment (e.g. puberty suppressing hormones) and others receive a treatment that looks the same (a placebo) that doesn't contain any active medicine. A double-blind design means that neither the participants or the researchers know which participants have been given the real medicine and which have been given the placebo. This type of design can help researchers see whether the real treatment is effective, by minimising psychological factors, for example, when a participant feels better because they believe they are receiving a real treatment (this is called the 'placebo effect').

PATHWAYS TRIAL uses a different trial design, where both groups receive an active treatment but it is delivered in different ways to the two groups. It will not use a placebo-controlled double-blind design because it is not possible for the participants or researchers to remain blind to the treatment effects for any significant period of time. The purpose of this intervention is to stop puberty, and it is well-documented to be an effective treatment for this outcome. The participants and researchers would therefore become unblinded to their treatment allocation, i.e., know whether they were receiving the real treatment, as the development (or not) of secondary sex characteristics would become obvious. Also, for birth-registered females, puberty suppression will stop their periods, so they will know very soon which group they are in.

Finally, it may benefit the young people receiving puberty suppressing hormones to know that they are having the treatment, and that their bodies will not start to change. Knowing that puberty is being suppressed may reduce mental health symptoms or improve quality of life This would be a real effect and would be important to measure.

3.4 Why can't research rely on retrospective records from gender services who have previously prescribed puberty suppressing hormones?

Retrospective studies are important, but they won't answer the question about the balance between benefits and risks of puberty suppressing hormones for several reasons.

Firstly, this is because we have seen an increase in the number of young people experiencing gender incongruence and seeking care in recent years. We think this group of young people are likely to be more diverse in terms of their personal characteristics and previous experiences and could have different support needs to those who have attended NHS gender services in the past. So, it's important to study the needs and experiences of this specific, current group of young people over time.

Secondly, to be able to understand the range of potential benefits or risks that young people receiving puberty suppressing hormones may experience, researchers need detailed records from when they were receiving puberty suppressing hormones as children or young people, using the same measures for everyone. Previous records which include the wide range of outcomes that will be assessed in PATHWAYS TRIAL are not available.

Thirdly, young people receiving puberty suppression in the new Gender Service will also get comprehensive non-hormonal care at the same time, which is important to factor in. These changes in other treatments means they might respond differently to puberty suppressing hormones.

Finally, observational data cannot show a cause-and-effect relationship meaning it cannot determine whether any observed benefits or harms are a result of the puberty suppressing hormone treatment, or whether they are attributable to other factors, either about the participants or other aspects of the care they receive including psychological support. A randomised controlled trial helps to eliminate some of these biases and confounding factors, allowing for stronger conclusions about the benefits or harms caused by the treatment.

3.5 Have there been other similar studies?

This is the first randomised controlled trial of puberty suppressing hormones. The study follows the recommendation from the Cass Review that the balance between benefits and risks should be evaluated in a clinical trial. This recommendation is supported by two independent reviews of research on puberty suppressing hormones for gender incongruence[3],[4] which concluded that there is a lack of high-quality longitudinal studies to inform patients and clinicians about the outcomes of puberty suppressing hormone treatment among young people with gender incongruence.

3.6 Will PATHWAYS TRIAL be stopped if a young person experiences an adverse impact?

The safety of participants will be closely monitored throughout the study. Adverse effects can vary in severity, and any impact on a young person's health and wellbeing will be assessed by the clinical team. If needed, the young person's treatment with puberty suppressing hormones can be paused or stopped, and they will receive appropriate medical and psychological support. Significant side effects will all be reported to the regulatory authorities as well as the Data Monitoring Committee, described below (Section 5.5).

As with any other clinical trial, PATHWAYS TRIAL as a whole could be stopped early if new safety information emerges, or on the advice of the independent Data Monitoring Committee, Programme Steering Committee, regulatory authorities, or the Research Ethics Committee. It may also be discontinued by the Sponsor or Chief Investigator if continuing the study is no longer considered safe or appropriate.

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[3] Miroshnychenko, A. (2025). Puberty blockers for youth experiencing gender dysphoria: A systematic review and meta-analysis. *Arch Dis Child*. https://doi.org/10.1136/archdischild-2024-327909

[4] Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: a systematic review. *Arch Dis Child*. https://doi.org/10.1136/archdischild-2023-326669

If the trial is ever discontinued early for any reason, all active participants currently taking part will be contacted by the Gender Service to discuss next steps and available options. They would continue to receive appropriate routine care and support within the service, and the relevant regulatory and ethics bodies would also be formally notified.

4 PATHWAYS CONNECT

4.1 What is PATHWAYS CONNECT?

PATHWAYS CONNECT is a study of brain development and cognition (thinking, learning and memory) in young people with gender incongruence. It compares young people enrolled in PATHWAYS TRIAL (and offered puberty suppressing hormones either immediately or after one year) to young people from PATHWAYS HORIZON who are not receiving puberty suppressing hormones. This group of young people recruited from HORIZON into CONNECT are referred to as *HORIZON INTENSIVE* because they are studied more intensively than other young people participating in HORIZON.

4.2 What is the aim of PATHWAYS CONNECT?

As described above (Section 1.3) adolescence and puberty is a time of rapid brain development and gains in abstract thinking, memory and organisation. There is evidence that these changes are affected by both chronological age and the development of puberty[5]. We don't know whether suppressing puberty in gender incongruence affects brain development and cognition because it has never been properly studied.

4.3 What will happen in PATHWAYS CONNECT for young people who chose to take part in TRIAL?

When young people and their parents/legal guardians consent to participate in TRIAL, they will also be told about CONNECT and asked whether they are interested in participating. All young people in TRIAL already participate in cognitive assessments as part of outcome monitoring. For those who agree, they will have brain scans at three time points: at the start of the study and before starting puberty suppressing hormones, (if in the immediate group), at one year and at two years at the end of the study. The scans will take an hour or less and all will be done at King's College London in South London. The study will pay travel and related expenses for young people and a parent/legal guardians as well as a £15 thank you voucher to young people for each scan.

4.4 What will happen in PATHWAYS CONNECT for young people in HORIZON INTENSIVE?

We will approach some of the young people participating in HORIZON to ask if they are interested in being part of PATHWAYS CONNECT. This group should be similar to TRIAL

[5] Goddings, A. L., Mills, K. L., Clasen, L. S., Giedd, J. N., Viner, R. M., & Blakemore, S. J. (2014). The influence of puberty on subcortical brain development. *Neuroimage*. https://doi.org/10.1016/j.neuroimage.2013.09.073

participants, in terms of birth-registered sex, age or stage of pubertal development, which NHS Children and Young People's Gender Service they are attending and whether they are neurodivergent. This means only some HORIZON participants will be approached.

HORIZON participants only complete questionnaire measures. Therefore, young people in HORIZON INTENSIVE will be asked to participate in cognitive assessments, brain scanning, bone scanning and blood measures of physical health at two time-points, two years apart. There are thank you vouchers for each different assessment. Travel and related expenses are paid for young people and a parent/legal guardians.

4.5 How many participants will be involved in PATHWAYS CONNECT?

PATHWAYS CONNECT will recruit 150 young people from PATHWAYS TRIAL. It will recruit 300 young people from PATHWAYS HORIZON into PATHWAYS INTENSIVE. Of the 300, only 100 are needed to participate in the brain scanning component.

4.6 Do PATHWAYS participants have to take part in PATHWAYS CONNECT?

No, participation in CONNECT is entirely voluntary and does not affect participation in either PATHWAYS TRIAL or PATHWAYS HORIZON. It also does not affect young people's routine care in the Gender Service or anywhere else in the NHS. Young people participating in PATHWAYS CONNECT can withdraw at any point and do not need to give a reason why.

5 Oversight and results

5.1 When will the results be available?

Currently, the trial is due to run for 5.5 years. We aim to publish the main results, including primary and secondary outcomes, in a peer-reviewed, open-access medical journal within 12 months of the trial's completion. We will ensure the findings are communicated in an accessible way to the public and interested groups. We will do this through our recruitment sites, interest groups, community events, the study website and the media. The findings will also be publicised at national or international scientific conferences. We do not plan to analyse the results until the study is complete.

5.2 Who appointed the study team to do this research?

The PATHWAYS Study was commissioned and funded by NHS England through the National Research Collaboration Programme (NRCP) in partnership with the National Institute for Health and Care Research (NIHR), following recommendations from the independent Cass Review to build more a robust evidence base for clinical care.

- Professor Emily Simonoff, at King's College London, was appointed as Chief Investigator to provide clinical and scientific leadership.
- Dr Michael Absoud is the Deputy Chief Investigator.
- Professor Richard Emsley is the Trial Statistician.

5.3 Who is responsible for the management of the study?

- The King's Clinical Trials Unit are leading on data management and analysis.
- The study is co-sponsored by King's College London and South London and Maudsley NHS Foundation Trust.

5.4 What approvals have been obtained for the study?

NHS England commissioned and funded the study in partnership with the National Institute for Health and Care Research (NIHR). The study has undergone a comprehensive review of the science by independent scientists advising NIHR. These include independent academic peer reviewers and NIHR funding committee consideration.

PATHWAYS TRIAL and PATHWAYS CONNECT have received full regulatory approvals from the Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA).

5.5 How is independent oversight ensured?

The research will be overseen by two independent committees: a Data Monitoring Committee, and a Programme Steering Committee, who will continue to monitor the safety and wellbeing of participants throughout the duration of the trial. The Committees will be convened according to the Research Governance Framework set out by NIHR.

5.6 How are people with lived experience involved in the study development?

We have consulted young people with lived experience and parents/caregivers from early in the study's development. We will continue to involve our advisory board of young adults and parents throughout the study's development, including when sharing our research findings.

PATHWAYS has Advisory Groups made up of young adults with lived experience as well as parents/caregivers. The Advisory Groups are convened by the National Children's Bureau for the PATHWAYS research team. The Advisory Groups will contribute to the design, implementation, and interpretation of study findings.