PATHWAYS Trial – Key Facts

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1. About the PATHWAYS TRIAL

What is PATHWAYS Trial?

The PATHWAYS Trial aims to provide the NHS with better evidence about the potential benefits and risks of puberty suppression to treat young people with gender incongruence to improve future care.

The safety and welfare of young people is the highest priority for the PATHWAYS research team, and the study has been carefully designed with this in mind.

The design of PATHWAYS Trial has been carefully reviewed by independent researchers and has been approved by the UK's health research regulators, the HRA and MHRA. There is also considerable external oversight of the study, including a panel of independent experts and those with lived experience

Only about 5% of young people attending NHS gender services will be eligible to receive puberty suppression as part of the clinical trial, the rest will continue to receive comprehensive psychological and social support. Their outcomes will be measured in a study called PATHWAYS Horizon.

There is a strict eligibility criteria for PATHWAYS Trial – including that young people will have had a diagnosis of gender incongruence for two years or more, and will already have engaged significantly with psychological and social interventions.

What is gender incongruence?

Gender incongruence is when a person's gender identity does not match the sex they were registered as at birth. For some people, this can cause significant distress, especially during puberty.

Under the World Health Organization's ICD-11 diagnostic criteria, the experience must be persistent over time, including for at least two years in children and young people before diagnosis.

While gender incongruence has been recognised for centuries, 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. However, there is not enough research to understand the outcomes of these different types of treatment, and the result of the PATHWAYS studies will help us understand which are effective.

Why is a clinical trial of puberty suppression needed?

The independent Cass Review found that there is not enough strong evidence to know for certain whether puberty-suppressing hormones (sometimes called puberty blockers in public discussions) help or harm young people with gender incongruence.

The Review said that previous research had important limitations and did not provide clear answers.

Puberty suppressing hormones have been prescribed to many thousands of young people with gender incongruence around the world. They have also been prescribed for over 30 years to young people with early onset puberty.

It is thought that if there were any serious short-term health concerns, they would have been picked up by doctors treating these young people.

However, there has never been a clinical trial to assess benefits and harms of puberty suppression in a robust research environment. PATHWAYS Trial will be the first randomised controlled clinical trial of puberty suppression to be carried out.

A randomised controlled trial is the best way to determine whether puberty suppression leads to overall benefit, no benefit, or harm. This type of study can compare outcomes more reliably than looking at past records alone.

Randomised controlled clinical trials are commonly used to understand the benefits and risks of a medicine, including for participants under the age of 18.

The need for a clinical trial of puberty suppression for young people with gender incongruence is supported by two independent reviews of existing evidence, which found that there is currently a lack of high-quality, long-term studies on the use of puberty-suppressing hormones in this group of young people. Among the existing studies, the findings were inconsistent in whether they showed overall benefit or not. As a result, patients, families, and healthcare professionals have limited evidence to guide decisions about treatment and its potential outcomes.

2. Current Access to Puberty Suppression

Are young people accessing puberty suppressing hormones in the UK at the moment?

The UK government was concerned about the lack of evidence around puberty suppression for gender incongruence. So they put in place a ban of the use of puberty suppressing hormones for young people with gender incongruence except as part of a clinical trial where their health could be closely monitored.

In the UK, since the puberty suppressing hormone ban came into effect, NHS gender services have seen increasing reports of unregulated private and online prescribing of puberty suppressing hormones for young people with gender incongruence.

These young people have had access to puberty suppressing hormones without the comprehensive health monitoring and psychosocial support that those taking part in PATHWAYS Trial will receive.

How many young people attending NHS gender services will get access to puberty suppressing hormones?

The majority of young people attending the new NHS Children and Young People's Gender services will receive psychological and social support only.

However, it is thought that, for a very small number of young people, psychological and social support will not be enough to help their gender distress.

These are young people who have had long-term gender incongruence that significantly affects their mental health and ability to participate in day to day activities, such as going to school or attending family or social occasions.

This group make up a small number of young people. the group that may be eligible for puberty suppressing hormones is likely to be around 5% (or one in 20 of young people attending NHS Gender Services, approximately 226 young people.

Even after PATHWAYS Trial begins, the majority of young people attending NHS Children and Young People's Gender Services will receive psychological and social support only. The outcomes of these young people will be studied in another PATHWAYS study that has already started; PATHWAYS Horizon is expected to involve 3000 participants and follow them for 5 years.

3. Evidence and Research

What do we know already about puberty suppressing hormones?

Despite puberty suppressing hormones being widely prescribed, there is uncertainty about:

- Whether puberty suppression improves emotional wellbeing, distress, daily functioning, or quality of life.
- Possible effects on physical health, including on bone development.
- Possible effects on brain development and thinking skills.

Because of these unanswered questions, the Cass Review, the Commission on Human Medicines, and the UK Parliament all concluded that a carefully designed clinical trial is needed.

Why is a trial needed if we have data from people who took puberty suppressing hormones in the past?

Looking at past records alone cannot show whether a treatment directly *caused* a particular outcome, and it cannot answer questions about how the **new** NHS service model is working. Both a study of retrospective data and a prospective clinical trial are needed.

Are there any studies investigating non-medical support for young people with gender incongruence?

Three other PATHWAYS studies are being carried out in parallel to the clinical trial. These studies will look at the impact of psychological and social interventions for young people with gender incongruence, and also in more detail about the impact on brain development, and they are:

PATHWAYS HORIZON is a longitudinal observational study of all young people attending the NHS Children and Young People's Gender Services who want to take part. It is the largest part of the PATHWAYS study, and will explore the wellbeing of young people, including their mental and physical health and experiences, and how these change (or not) as they grow up. This study has been approved by regulators and has begun. 3000 young people are expected to take part.

PATHWAYS CONNECT will look at young people's thinking and brain development, and will follow both those who are, and are not, taking puberty suppressing hormones.

PATHWAYS VOICES involves speaking to young people about their experiences of living with gender incongruence and of their care in the NHS Children and Young People's Gender Services including, for some, taking puberty suppressing hormones. We will talk to young people and parents/caregivers several times while they are attending the Services. We will also find out from staff working within the Services about what they think helps.

4. Taking Part in the Trial

Who is eligible for PATHWAYS Trial?

To be eligible for the puberty suppression clinical trial, a young person must meet a number of criteria. These include:

- Have a diagnosis of gender incongruence based on international diagnostic criteria (known as the ICD-11).
- Have experienced gender incongruence for more than two years.
- Have already received substantial psychosocial support within the new gender services.
- Want puberty suppression as a treatment option.
- Have agreement from their parent or legal guardian.
- The doctors and psychologists responsible for their care in the NHS Gender Services need to think they have a good chance of benefitting from puberty suppression.
- Birth-registered girls must be at least 11 years old and birth-registered males at least 12 years old.

Eligibility is then reviewed by both the young person's clinical team and an independent national multidisciplinary team. Both have to agree that the young person has a good chance of benefitting from puberty suppression.

Before joining the study, young people will undergo health checks to ensure the treatment is suitable for them. These checks include physical examinations, blood and urine tests, heart monitoring (ECG), bone health scans, and assessments of puberty stage.

How will young people receive puberty-suppressing hormones?

Puberty-suppressing hormones are given as injections. The most commonly used medicine is Triptorelin, which is usually administered every six months, although some young people may receive smaller doses more frequently. Alternative medicines may be used if side effects occur.

Participants in the study will either begin treatment immediately or after a one-year delay. Those in the delayed group will start receiving injections after one year.

Are participants paid to take part in PATHWAYS Trial?

It is usual practice for clinical research studies such as PATHWAYS to offer recognition for taking part in research studies. This is to acknowledge participant's time rather than incentivise them

to participate. Any proposal to do this is included in the research protocol which is reviewed by the Health Research Authority and the Research Ethics Committee.

Participants taking part in the PATHWAYS TRIAL – the clinical study of puberty-suppression hormones involving 226 young people - receive £30 for the in-depth cognitive assessments, and £15 for brain imaging – to a maximum of £135. They do not receive any financial compensation for enrolling, physical health tests or completing mental health questionnaires. Parents/legal guardians do not receive compensation for filling out research questionnaires.

Why isn't there a placebo for this study?

It isn't possible to use a placebo for puberty suppression because it will be clear to both the young people and their clinical team whether they are receiving treatment.

A treatment delay is being used instead which will compare an immediate start group compared to a delayed start (12-months) group. This allows comparison of a matched group who are receiving and not receiving treatment. This design is well recognized and has been approved by the health and medicines regulators and reviewed by a panel of independent experts.

5. Safety, Monitoring and Long-Term Follow-Up

How will participant safety be monitored?

The physical and mental health monitoring of participants taking part in PATHWAYS Trial is more extensive than any previous instance of children and young people being prescribed puberty suppressing hormones in the UK or internationally.

Throughout the study young people who take part will receive regular health monitoring, including:

- Physical health assessments.
- Blood and urine tests.
- Bone health monitoring.
- Cognitive (thinking and memory) assessments.
- Wellbeing questionnaires.
- Regular reviews with healthcare professionals
- Regular appointments with their NHS care team and young people will be encouraged to report any symptoms or side effects promptly.

What will the long term follow up options be?

Participants taking part in PATHWAYS Trial will be regularly reviewed for 2 years after their baseline assessment. During this time, they will complete research procedures every 3 to 6 months. After the first 2 years, all participants will be included in annual follow-ups throughout the study period.

Follow-up into adult life is also important and participants will 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. For those who want to stay on puberty suppressing hormones for longer, and where their doctors and the national Multidisciplinary Team agree, they may be able to continue in an extension study, where further research procedures to measure safety and benefits will continue to be collected.

What health risks does puberty suppression in young people with gender incongruence pose?

Risks of puberty suppression in young people with gender incongruence have been overstated in public debate in many instances

Risks to the health of young people receiving puberty suppressing hormones (including claims of unavoidable infertility, permanent cognitive impairment, or irreversible bone damage) that are sometimes cited are not supported by current evidence. This includes lack of evidence about:

Bone health: Studies show reductions in bone mineral density scores during the time a young person receives puberty suppressing hormones, but absolute levels typically remain within the population (expected) range and recovery of bone density is expected once treatment stops The PATHWAYS Trial includes careful monitoring of all young people taking part.

Follow-on treatments such as cross sex hormones: In the past, young people often transitioned from puberty suppression to gender-affirming hormones without careful review of their needs. The PATHWAYS Trial concerns puberty suppression only; access to gender-affirming hormones (which is governed and commissioned separately) is not part of this trial**.**

Fertility: Puberty suppressing hormones stop the body from releasing eggs or making sperm while someone is taking them. This means a young person would not be able to cause a pregnancy or become pregnant during treatment. There is currently no evidence that puberty suppression affects fertility in the long term, despite these drugs having been widely prescribed for both gender incongruence and precocious puberty. Cross-sex and gender-affirming hormones, which may be prescribed after puberty suppression, do have effects on fertility. As a result for young people aged 16 and over (and, in certain circumstances, younger adolescents) fertility preservation options such as egg retrieval, sperm banking, or ovarian/testicular tissue cryopreservation can be discussed and offered where clinically feasible and desired. These discussions form part of the routine counselling provided by the new NHS Children and Young People's Gender Services and are available to families who wish to consider them.

Cognition: There is no evidence that the use of puberty suppression in children and young people has any negative impacts on cognitive function. This is despite puberty suppressing hormones having been prescribed widely. Despite this, PATHWAYS Trial and Connect studies will carefully investigate any changes to cognitive function - including using cognitive assessments and brain scans.

6. Governance, Regulation and Oversight

How has the PATHWAYS Trial been reviewed?

All parts of the PATHWAYS study have been designed to meet rigorous scientific and ethics standards

PATHWAYS Trial has been through extensive review, and has all the necessary approvals in place to show that the trial design is robust enough to answer the research question; and is both ethical and safe:

- The study first underwent a comprehensive review of the science by independent scientists advising NHS England and NIHR.
- PATHWAYS Trail was then reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA), who sought independent advice from the Commission on Human Medicines (CHM); and by the Health Research Authority and a Research Ethics Committee. PATHWAYS Trial received all necessary approvals from this process.
- The MHRA suggested some additional safeguards in February 2026. These suggestions were not initiated by new scientific evidence. After a series of scientific meetings between the MHRA and the PATHWAYS research team, a modified protocol was submitted to the MHRA, HRA and REC for regulatory approvals. The MHRA also sought further advice from the CHM. The trial received all necessary approvals of the modified protocol in June 2026.
- PATHWAYS Trial will be overseen by independent oversight boards made up of clinicians, scientists and lay members with lived experience external to the research project. They are also informed by two independent lived experience advisory boards of young adults and parents.
- A request for judicial review concerning the lawfulness of the regulatory decisions made by health regulators in approving PATHWAYS Trial was made. The request was refused.

Why did the MHRA have concerns about the study, and the government 'pause' the study?

The PATHWAYS research team received a letter from the Medicines and Healthcare Products Regulatory Agency (MHRA) on 16th February 2026 asking us to consider several changes to the PATHWAYS Trial protocol.

The MHRA, the Health Research Authority (HRA) and the Research Ethics Committee (REC), had already approved the Trial protocol in November 2025. The MHRA letter did not contain any new scientific data or evidence to underpin the suggested modifications.

We have worked extensively and openly with the MHRA to understand and resolve the questions they raised about PATHWAYS Trial in February. We have strengthened patient information connected to the trial, clarified safety monitoring, and introduced a minimum age requirement, however there were no major changes to the design or conduct of PATHWAYS Trial. These changes were approved by the MHRA, the HRA and the REC in June 2026.

7. Results and Future Impact

What do the research team think the results will be, and will the findings overturn the puberty suppressing hormone ban?

The research team have no preconceived ideas about the likely outcome of PATHWAYS Trial. They are approaching it as with any other clinical trial, and with an open-minded view of what the study will find.

It is possible that the findings will find that puberty suppressing hormones should, or should never, be prescribed. Or the study might find that there is a subset of young people for whom benefits override risks.

The main aim is to provide a robust evidence base to guide NHS to best support young people with gender incongruence, guided by research.

Findings from the PATHWAYS studies will be made widely available and published in peer reviewed journals.

We need to make sure we are clear headed in our approach to supporting young people with gender incongruence. The research team fully understands that there are ongoing societal discussions about gender transition, but this research is about healthcare and aims to sit outside of the politics. Most affected young people and their families we have spoken to just want to know what is the best care option for them based on evidence.

8. Further information

Where can I find out more?

The PATHWAYS research team have made detailed information about the study available online. Visit the study page to read an FAQs, the study protocol, patient information leaflets and other background information.

To read more about PATHWAYS Horizon study, please visit the study page: https://www.kcl.ac.uk/research/pathways-horizon