

# Best practice for hormonal replacement of puberty in adolescent and young adult men with absent or incomplete puberty

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## Plain English summary of protocol

### Background and study aims

Infertility affects 15% of couples. The management of male infertility is challenging, particularly in severe forms of hormone deficiency. These hormones are specific signals produced by the brain, which direct the development of the testicles or ovaries. Patients who are unable to produce these signals (named gonadotropin hormones) have a condition called gonadotropin deficiency (GD).

For adult men with GD, treatment for fertility is often unsuccessful. This is because hormones drive the development of the testicles in childhood, a vital process to enable later sperm production. Despite adult hormone replacement, individuals may suffer infertility in addition to chronic health and psychological issues.

Standard treatment for lack of puberty in adolescent males with GD is with testosterone. This helps with physical development, but not with testicular development or sperm production. PPI work with patients and carers has highlighted the importance for young men with GD of adequate pubertal development, testicular maturity and the ability to make sperm.

In contrast, puberty replacement with gonadotropin hormones enables physical maturity and a growth spurt, as well as specific testicular growth, to occur. These medications are currently used in adult patients with GD within fertility services, but can be used in puberty to allow reproductive development at the appropriate age.

This study will assess the effectiveness of gonadotropin therapy for puberty induction in young males (12-35 years) with GD. We will address the best combination of gonadotropins to help patients make sperm and the reasons for differences in response to these medications between patients. We will interview patients to understand their experiences of receiving gonadotropin therapy.

### Who can participate?

Male patients aged between 12 and 35 years with gonadotropin deficiency

### What does the study involve?

The Partial Treatment group will receive subcutaneous gonadotropin injections of BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per

week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months. The Partial Control group will receive subcutaneous gonadotropin injections of hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months AND IF criteria for rescue therapy is met at 9-12 months will receive subcutaneous gonadotropin injections of recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 6-15 months. The Severe Treatment group will receive subcutaneous gonadotropin injections of recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 2 months, followed by BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 16-22 months. The Severe Control group will receive subcutaneous gonadotropin injections of BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months. All groups will be followed up at 4-6 monthly study visits with clinical examination and auxology, blood tests and testicular ultrasound. Once testicular development has reached a threshold of 10-12 ml volume, semen analysis will be carried out. Pre- and post-treatment quality of life will be assessed by questionnaire and qualitative interviewing will be offered. Whole genome testing will be carried out at baseline.

What are the possible benefits and risks of participating?

There are potential benefits of participating in the study, including for physical development and well-being. Participants will receive access to treatment with gonadotropins, which results in physical development that is over and above what would occur if receiving the current NHS standard of care, namely testosterone replacement. The main visible change participants would be aware of is the growth and development of the testicles. In addition, we anticipate that receiving gonadotropin therapy in puberty will result in improved fertility and psychosexual benefits in adult life.

The medications given in this trial are provided to participants to take home and to self-administer. Usually, the young person will give themselves the subcutaneous (just under the skin) injection, or their parent or caregiver will do this for them. The injections are given with a very small and thin needle and are usually pain-free.

Risks of these medications are low, with the most frequently occurring adverse effects of mild gynaecomastia (male breast development), acne or injection site reaction experienced in 8.1%, 6% and 5% of patients, respectively, in our recent review of the published studies on the use of these treatments. This is confirmed by a review of male patients with GD from our service receiving these therapies in the past 12 months, in whom 1 in 20 have developed mild gynaecomastia, and no patients have reported other adverse effects. It is important to note that these clinical features also occur in young men undergoing spontaneous puberty or those undergoing pubertal induction with testosterone.

The protocol has been designed with input from patients and carers and with awareness of potential distress that may arise during involvement activities. The burden of activities has been minimised wherever possible and closely mirrors the standard assessments that occur in NHS practice for young people with GD. Our work with patients and the public has highlighted how motivated this patient group is to improve therapies for this underserved condition, and that families often seek out specialist clinicians who can offer gonadotropin therapy for pubertal induction, sometimes travelling across the country for treatment. However, we are also mindful of the need for sensitivity in recruiting participants to this study, to balance needs of the young person with those of their family/carers, and that a proportion of children and young people

with GD will opt to follow standard treatment protocols for GD with testosterone as these are more straightforward.

For younger participants, the acceptability of semen analysis is important to explore. The protocol for collecting semen for analysis has become more straightforward for boys and young men, with collection within the patient's home and then transfer of the sample to the lab for analysis. This is much more acceptable than the previous system of having to provide a sample at the testing centre. Our practice is to discuss the purpose and process of semen analysis from the beginning of the patient's treatment and repeat the information on a regular basis, to allow the patient to express any concerns or fears, answer questions and to ensure they are psychologically well prepared for the process once ready physically.

Where is the study run from?

Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?

June 2025 to January 2030

Who is funding the study?

National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?

1. Dr Sasha Howard, s.howard@qmul.ac.uk
2. Shared team inbox, pingstudy@qmul.ac.uk

## Contact information

### Type(s)

Scientific, Principal investigator

### Contact name

Dr Sasha Howard

### Contact details

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### Type(s)

Public

### Contact name

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## **Additional identifiers**

### **Clinical Trials Information System (CTIS)**

Nil known

### **Integrated Research Application System (IRAS)**

1009018

### **ClinicalTrials.gov (NCT)**

Nil known

### **Protocol serial number**

CPMS 58941

## **Study information**

### **Scientific Title**

Pubertal induction with gonadotropin treatment in males with hypogonadotropic hypogonadism: the PinG study

### **Acronym**

PinG

### **Study objectives**

Objectives:

1. To compare the capacity to make sperm following treatment to replace puberty, with either a single (hCG) medication or a combination of two different medications (rFSH and hCG), in male patients who are partially affected with gonadotropin deficiency (GD).
2. To compare the capacity to make sperm following treatment to replace puberty, with or without prior treatment with rFSH, followed by a combination of two different medications (rFSH and hCG), in males who are severely affected with GD.
3. To compare further markers of success in replacement of puberty (including size of their testicles, blood markers of testicle function and quality of their sperm) in patients who are partially affected with hypogonadotropic hypogonadism (HH), who have received either a single (hCG) medication or a combination of two different medications (rFSH and hCG).
4. To compare further markers of success in replacement of puberty (including size of their testicles, blood markers of testicle function and quality of their sperm) in patients who are severely affected with HH, with or without prior treatment with rFSH, followed by a combination of two different medications (rFSH and hCG).
5. To assess differences in how well patients with HH respond to these treatments between patients who have different gene changes responsible for their condition.
6. To assess quality of life in patients with HH and their carers, before and after these treatments to replace puberty.

### **Ethics approval required**

Ethics approval required

**Ethics approval(s)**

notYetSubmitted, ref: 25/LO/0504

**Study design**

Open randomized controlled trial

**Primary study design**

Interventional

**Study type(s)**

Efficacy

**Health condition(s) or problem(s) studied**

Gonadotropin deficiency secondary to hypogonadotropic hypogonadism or pituitary hormone deficiency

**Interventions**

The PinG study is an open-label randomised controlled study. The protocol is stratified according to disease severity, into those participants with partial congenital hypogonadotropic hypogonadism (CHH) as described according to the inclusion criteria listed and maximal testes volume  $\geq 4$  ml, and participants with severe CHH as described according to the inclusion criteria and maximal testes volume  $< 4$  ml.

Partial Treatment arm – will receive subcutaneous gonadotropin injections of BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months.

Partial Control arm - will receive subcutaneous gonadotropin injections of hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months AND IF criteria for rescue therapy is met at 9-12 months will receive subcutaneous gonadotropin injections of recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 6-15 months.

Severe Treatment arm - will receive subcutaneous gonadotropin injections of recombinant (r) FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 2 months, followed by BOTH recombinant (r)FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 16-22 months.

Severe Control arm - will receive subcutaneous gonadotropin injections of BOTH recombinant (r) FSH (follitropin alpha) at dose of 75-225 IU with a frequency of three times per week (increased to alternate days if required) for 18-24 months AND hCG (choriogonadotropin alfa) at dose of 500-200 IU with a frequency of once-twice per week for 18-24 months.

All arms will be followed up at 4-6 monthly study visits with clinical examination and auxology, blood tests and testicular ultrasound. Once testicular development has reached a threshold of 10-12 ml volume, semen analysis will be carried out. Pre- and post-treatment quality of life will

be assessed by questionnaire and qualitative interviewing will be offered. Whole genome testing will be carried out at baseline.

Within both the partial GD and severe GD groups, participants will be randomised within REDCap in a 1:1 ratio.

## **Intervention Type**

Drug

## **Phase**

Phase III

## **Drug/device/biological/vaccine name(s)**

Follitropin alfa, chorionic gonadotropin

## **Primary outcome(s)**

Capacity for spermatogenesis is measured by total sperm concentration  $\geq 1 \times 10^6/\text{ml}$  on semen analysis at 18 months of treatment

## **Key secondary outcome(s)**

1. Testicular development measured by testicular volume via orchidometer at 0, 6, 12, 18 (+/- 24) months of treatment
2. Testicular development measured by Inhibin B concentration in blood samples at 0, 6, 12, 18 (+/- 24) months of treatment
3. Sperm quality measured by maximal sperm concentration on semen analysis at 18 (+/- 24) months of treatment
4. Treatment length to achieve spermatogenesis measured by months to reach a total sperm concentration  $\geq 1 \times 10^6/\text{ml}$  on semen analysis at 18 + 24 months of treatment
5. Genetic contribution to response to treatment measured by whole genome sequencing at baseline with analysis of correlation of pathogenic variants identified with primary outcomes
6. Quality of life changes after treatment measured by questionnaire at baseline and end of treatment

## **Completion date**

31/01/2030

## **Eligibility**

### **Key inclusion criteria**

1. Age  $\geq 12$  and  $< 35$  years
2. Males
3. Participant or their parent/carer is willing and able to give informed consent for participation, with informed assent from the participant if  $< 16$  years
4. Able and willing to comply with all study requirements, including ability to participate in study for a minimum of 18 months
5. Willing to allow their General Practitioner (GP) to be notified of participation in the study
6. Diagnosis of gonadotropin deficiency (hypogonadotropic hypogonadism) by biochemical criteria (low or undetectable basal LH and FSH with low or undetectable testosterone)
7. Additional confirmatory features (at least one of):
  - 7.1. Inhibin B  $< 150 \text{ pg/ml}$
  - 7.2. Red flags – small testes volumes, cryptorchidism, micropenis, synkinesis, anosmia

7.3. Clinical hypogonadotropic hypogonadism with additional pituitary hormone defects (GH, TSH, ACTH deficiency)

7.4. Peak LH on GnRH stimulation testing of <5 IU/l

7.5. Diagnosis of congenital hypogonadotropic hypogonadism confirmed by genetic testing

7.6. MRI pituitary/ olfactory bulbs demonstrating anatomical abnormalities consistent with hypogonadotropic hypogonadism

8. Patient requiring treatment to induce or complete the induction of puberty

Additional inclusion criteria for partial GD:

1. Maximal testes volumes  $\geq 4$  ml

Additional inclusion criteria for severe GD:

1. Maximal testes volumes <4 ml

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Mixed

### **Lower age limit**

12 years

### **Upper age limit**

35 years

### **Sex**

Male

### **Key exclusion criteria**

1. Age <12 or  $\geq 35$  years

2. Females

3. Functional hypogonadism due to low caloric intake, excessive exercise or chronic disease

4. Primary hypogonadism

5. Constitutional or self-limited delayed puberty

6. Active hypothalamic or pituitary tumour

7. Uncontrolled non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders)

8. Hypersensitivity to the active substance or excipients

### **Date of first enrolment**

31/08/2025

### **Date of final enrolment**

31/03/2028

## **Locations**

**Countries of recruitment**

United Kingdom

England

Scotland

**Study participating centre****Barts Health NHS Trust**

The Royal London Hospital

80 Newark Street

London

United Kingdom

E1 2ES

**Study participating centre****Uclh**

250 Euston Road

London

United Kingdom

NW1 2PQ

**Study participating centre****Great Ormond Street Hospital**

Great Ormond Street

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United Kingdom

WC1N 3JH

**Study participating centre****Hammersmith Hospital**

Du Cane Road

Hammersmith

London

United Kingdom

W12 0HS

**Study participating centre****St Mary's Hospital**

Praed Street

London

United Kingdom  
W2 1NY

**Study participating centre**

**Royal Victoria Infirmary**

Queen Victoria Road  
Newcastle upon Tyne  
United Kingdom  
NE1 4LP

**Study participating centre**

**Birmingham Children's Hospital**

Steelhouse Lane  
Birmingham  
United Kingdom  
B4 6NW

**Study participating centre**

**Alder Hey Hospital**

E Prescott Rd  
Liverpool  
United Kingdom  
L14 5AB

**Study participating centre**

**Sheffield Childrens Hospital**

Western Bank  
Sheffield  
United Kingdom  
S10 2TH

**Study participating centre**

**Royal Hospital for Children and Young People**

50 Little France Crescent  
Edinburgh  
Lothian  
United Kingdom  
EH16 4TJ

**Study participating centre**  
**Royal Hospital for Sick Children (Glasgow)**  
1345 Govan Road  
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United Kingdom  
G51 4TF

**Study participating centre**  
**Nottingham Children's Hospital**  
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Derby Rd  
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NG7 2UH

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**Study participating centre**  
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**Study participating centre**  
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Westminster Bridge Road

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**Study participating centre**  
**Southampton Children's Hospital**  
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Tremona Road  
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## Sponsor information

**Organisation**  
Queen Mary University of London

**ROR**  
<https://ror.org/026zzn846>

## Funder(s)

**Funder type**  
Government

**Funder Name**  
National Institute for Health and Care Research

**Alternative Name(s)**  
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**  
Government organisation

**Funding Body Subtype**  
National government

**Location**  
United Kingdom

# Results and Publications

## **Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study will be available upon request from the study team (pingstudy@qmul.ac.uk), if the request is from teams conducting relevant research in the subject area and is deemed reasonable and appropriate by the study team. No data will be released for sharing until at least 18 months after study completion. All tagged identifier fields will be removed from the dataset prior to export and transfer to ensure that no participant identifiable data is transferred or accessed. Only data from participants who have consented to data being shared will be included (this is an optional consent on the study ICF). Deidentified study data can be shared via secure STFP transfer. Data requests will be available for a minimum of 18 months after study close.

## **IPD sharing plan summary**

Available on request