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The growth hormone deficiency reversal trial

Submission date
16/03/2021

Recruitment status
Stopped

Registration date
18/03/2021

Overall study status
Stopped

Last Edited
12/09/2024

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims:
Growth hormone (GH) is a hormone essential for normal growth and development. If a child doesn't have enough GH, the speed of growth is slower and final adult height reduced. Growth hormone deficiency (GHD) is a condition where the pituitary gland doesn't make enough growth hormone in childhood. GH treatment allows children with GHD to grow normally. GH is given as daily injections continued until the child reaches adult height. GH is usually given for 5-10 years and can cost £10,000-23,000 per patient per year.
Children are tested for GHD by measuring the highest amount of GH in the blood following a test. When GH production is checked after children reach their final height, some children are found to have normal levels of GH; these children therefore no longer have GHD. Some doctors think that this change occurs during puberty. Many pubertal children on GH therapy are assumed to no longer have GHD but doctors usually continue daily GH injections until the child reaches final adult height. Therefore some children continue to have potentially unnecessary, costly daily injections.
The aim of this 'GHD Reversal' study is to find out whether certain children can stop their GH injections at puberty and still reach a similar final adult height to those children who continue to have daily GH injections.

Who can participate?
Children with I-GHD whose stimulated GH levels are found to be normal when tested after they have entered puberty. After giving their consent, these children will be randomised (chosen by 50:50 chance by a computer) to either continue or stop their daily GH injections.

What does the study involve?
The study will test whether the children who stop their GH injections reach a similar final adult height to those children that continue their injections. Children will have 6-monthly trial assessments at their hospitals endocrine clinic where they will have blood samples taken (to look at the level of GH and the lipids in it) and other biometric data (e.g. height, weight) collected. These activities are already done as part of standard care for these children and the trial visits should be matched up to the child's usual visit schedule. At the first and last trial assessments children will have an X-ray of their non-dominant hand, and at some they will be asked to complete a short questionnaire about their quality of life (the CHU-9D questionnaire). At the last trial assessment children will have another GH test.

What are the possible benfits and risks of participating?
If a child is in the group who are not taking growth hormone, this would mean that they no longer need to have daily injections.
If a child is randomised to the group who are continuing with their growth hormone injections they may not directly benefit from taking part in the study, however the information we get from the study may help us to improve the treatment of young people with growth hormone deficiency in the future.
Taking part in this study is very unlikely to cause any child any discomfort or side-effects.
If a child is put in the group who stop their injections of growth hormone then their growth will be monitored closely. At the first sign that a child might be developing another shortage of growth hormone they will be retested and growth hormone treatment restarted.

Where is the study run from?
The Chief Investigator is Professor Mehul Dattani at University College London (UCL). UCL are also the Sponsor. The study is being coordinated by the Birmingham Clinical Trials Unit at the University of Birmingham.

When is the study starting and how long is it expected to run for?
June 2020 to November 2027

Who is funding the study?
National Institute for Health Research - Health Technology Assessment Programme (UK

Who is the main contact?
Professor Mehul Dattani, m.dattani@ucl.ac.uk
Mr Adam Khan, a.r.khan@bham.ac.uk

Study website
https://www.birmingham.ac.uk/research/bctu/trials/renal/ghd/trial-overview

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-001006-39

IRAS number
281209

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

IRAS 281209, HTA - NIHR127468

Study information

Scientific Title
Effect on final height of discontinuation vs continuation of growth hormone treatment in pubertal children: The Growth Hormone Deficiency Reversal Trial

Acronym
GHD Reversal Trial

Study objectives
Discontinuation of growth hormone medication (somatropin) at early puberty in children with isolated growth hormone deficiency results in a final height that is no worse than pubertal children who continue taking somatropin until final height is reached.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/04/2022, Wales REC3 (The Caerphilly Suite, Holiday Inn Cardiff North M4/J32, Merthyr Road, Coryton, Cardiff, CF15 7LH, United Kingdom; +44 (0)2922 941107; Wales.REC3@wales.nhs.uk), ref: 22/WA/0005

Study design
Multicentre interventional non-inferiority randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Participant information sheet not yet available

Health condition(s) or problem(s) studied
Isolated growth hormone deficiency in pubertal children

Interventions
Control arm: Standard care - Continuation of growth hormone medication (somatropin) as daily injections, until final height. Treatment will last from the point of randomisation, up until 6 weeks before final assessment (which is variable, as below).
Experimental arm: Discontinuation of growth hormone medication (i.e. stopping of daily

injections) during early puberty (unless GH treatment is required for clinical reasons) whilst they are in the trial.

Participants are randomised 1:1 between the control and experimental arms. Minimisation variables are trial centre, sex and Tanner stage: (B2 (females) or 6-<9 ml testicular volume (males) vs B3 (females) or 9-12 ml testicular volume (males). Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU).

Follow-up (the same duration in both arms) will continue until each patient reaches their 'near Final Height (FH)'. This is defined as a growth rate of less than 2 cm/year and an X-ray analysis via BoneXpert software, confirming that patients have reached a 'bone age' (a measure of skeletal growth) of 14 in females and 16 in males. It is expected that patients will reach their FH within 36 months, however, this may vary. As such, a standard follow-up duration has not been set for most patients. Follow-up will end for any patients that have not reached FH once the final patient reaches their 36-month assessment, to keep to the trial timeline.

Intervention Type
Supplement

Primary outcome measure
Height (cm) measured in Standard Deviation Score (FH SDS) at end of follow-up

Secondary outcome measures
1. Bone-related:
1.1. Bone age delay measured using BoneXpert X-ray analysis at end of follow-up
1.2. Bone age acceleration measured using BoneXpert X-ray analysis between enrolment and end of follow-up
1.3. Bone health index measured using BoneXpert X-ray analysis at end of follow-up
2. Biochemistry:
2.1. Serum IGF-1 and lipid profiles measured using trial site's usual testing methods at end of follow-up
2.2. Peak stimulated GH measured using insulin tolerance test or argnine test at end of follow-up
3. Adverse events measured using GHD Reversal Trial CRFs over follow-up duration
4. Health Economics:
4.1. Cost per percentage achieving Target Height measured using healthcare contacts costs (captured via GHD Reversal Trial CRFs) over follow-up duration
4.2. Cost per Quality Adjusted Life Year (QALY) gained, measured using CHU-9D questionnaire over follow-up duration
5. Qualitative Research: Trial acceptability (parents, patients and staff); reasons to decline the trial; parent and patient experience of the trial and treatment pathways, measured via interviews with parents, patients and site staff during the pilot phase of the trial

Overall study start date
01/06/2020

Completion date
30/11/2027

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
1. Initial diagnosis of I-GHD will have been made by either two GH stimulation tests (peak GH <6. 7µg/L) or one abnormal stimulation test with low IGF-1 (below normal range for sex & age), irrespective of sex-hormone priming for GH stimulation tests
2. Children with reversed I-GHD (peak GH ≥6.7 µg/L and a serum IGF-1 within normal reference range for sex and age) and a normal brain MRI (incl. small anterior pituitary)
3. Children in established puberty – Tanner stages B2/3 in girls & 6-12ml testes* in boys (as measured by orchidometer**)
4. Children will have discontinued GH treatment for a minimum of 6 weeks prior to re-testing
5. Children will have remained off GH therapy from time of re-test until randomisation
6. Ability to tolerate the administration of GH therapy
7. Ability to comply with trial schedule and follow up
8. Written informed consent obtained from the patient's parent/guardian and written assent obtained from patient (where age appropriate). Patients aged 16 years or older will provide their own written informed consent
*In the event of discrepancy between the size of an individual's testicles, the larger testicle should be used
**In the event that the size of a patient's testicle falls between the measuring beads of the orchidometer and it is not clear which bead the testicle is most similar to, the larger bead should be used

Participant type(s)
Patient

Age group
Child

Lower age limit
8 Years

Upper age limit
17 Years

Sex
Both

Target number of participants
138

Total final enrolment
5

Key exclusion criteria
1. Multiple pituitary hormone deficiency (hypopituitarism) with or without additional pituitary hormone supplementation
2. Known genetic cause of I-GHD
3. Organic GHD (mid-brain tumours, congenital mid-brain malformations, septo-optic dysplasia; radiotherapy to the total body or brain)

4. Ectopic posterior pituitary
5. Other indications for GH therapy
6. Receiving GH treatment during the (minimum 6 week) discontinuation period
7. Receiving prednisolone or dexamethasone for a period of 4 weeks or longer in the time period immediately prior to randomisation
8. Known history of persistent non-compliance with prescribed medication regimens
9. Pregnant or lactating
10. Any malignancy
11. Currently participating in another Clinical Trial of an Investigational Medicinal Product (CTIMP)

Date of first enrolment
01/08/2021

Date of final enrolment
09/05/2024

Locations

Countries of recruitment
Austria

England

United Kingdom

Study participating centre
Great Ormond Street Hospital
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
Alder Hey Children's Hospital
Eaton Road
Liverpool
United Kingdom
L12 2AP

Study participating centre
The Royal London Hospital
80 Newark Street

London
United Kingdom
E1 2ES

Study participating centre
Birmingham Children's Hospital
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Study participating centre
King's College Hospital
Denmark Hill
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SE5 9RS

Study participating centre
Royal Manchester Children's Hospital
Oxford Road
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M13 9WL

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Norwich
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NR4 7UY

Study participating centre
Nottingham Children's Hospital
Queen's Medical Centre, Derby Road
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NG7 2UH

Study participating centre
St James's University Hospital
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LS9 7TF

Study participating centre
Kepler Universitätsklinikum
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4020 Linz

Study participating centre
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Study participating centre
LKH-Universitätsklinikum Graz
Auenbrugger Platz 1
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor type
University/education

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ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/11/2028

Individual participant data (IPD) sharing plan
Requests for data generated during this study will be considered by BCTU (to bctudatashare@contacts.bham.ac.uk). Data will typically be available within six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the Chief Investigator and, where appropriate (or in absence of the Chief Investigator) any of the following: the Trial Sponsor, the relevant Trial Management Group (TMG), and independent Trial Steering Committee (TSC).

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of patient identifiable information. Any data transfer will use a secure and encrypted method.

IPD sharing plan summary
Available on request