Short Title – The GHD Reversal Trial

Full Title – The Growth Hormone Deficiency Reversal Trial: Effect on final height of discontinuation vs continuation of growth hormone treatment in pubertal children with isolated growth hormone deficiency – A non-inferiority randomised controlled trial

Site Initiation Visit

[Insert Trust Name]

[Insert Date]

Background

Background – The GHD Reversal Trial

- Growth hormone deficiency (GHD) occurs when the pituitary gland does not produce enough human growth hormone (HGH) – this is the commonest hormonal cause of short stature

- Around 500 children are diagnosed with growth hormone deficiency every year in the UK, of whom 75% have idiopathic, isolated GHD (I-GHD)

- To make the diagnosis of I-GHD in a short child, the National Institute for Health and Care Excellence (NICE) recommends at least two GH (growth hormone) stimulation tests (by measuring the peak GH concentration in the blood following an injection with a stimulating substance such as glucagon or insulin), which must both show a peak GH <6.7 µg/L

Background – The GHD Reversal Trial

- Children diagnosed with I-GHD are treated with daily GH injections until final height (FH) is reached
- GH treatment allows children with GHD to develop normally, however GH treatment can be expensive, with research suggesting daily injections incur an annual cost of £10,000 - £23,000 per child
- Between 26-88% of children, when re-tested once they've reached FH, are found to be producing sufficient endogenous GH not to have required the injections – i.e. their GHD has reversed
- Current practice is to continue treatment with daily injections of GH until FH is achieved
- These injections can be unpleasant, inconvenient for patients, utilise substantial NHS resources and leave the child and their families with a diagnostic uncertainty about the persistence of I-GHD

Purpose of the Trial

Purpose of the GHD Reversal Trial

The main aim of the GHD Reversal Trial is to assess whether children with early GHD reversal who stop (GH-) growth hormone therapy achieve a Final Height which is no worse than those continuing (GH+) growth hormone therapy.

Primary Outcome = Final Height in Standard Deviation Score

Put simply – In patients whose GHD has reversed, does stopping GH treatment have a meaningful effect on their final height?

Purpose of the GHD Reversal Trial

As part of the trial we will also assess a range of key secondary outcomes:

Growth-related –

- The proportion of children reaching normal adult height
- The proportion of children reaching mid-parental Target Height (TH)
- Difference in Target Height minus Final Height (FH) between GH+ and GH- groups

Purpose of the GHD Reversal Trial

As part of the trial we will also assess a range of key secondary outcomes:

Bone-related –

- Bone age delay at Final Height
- Bone age acceleration between enrolment and Final Height
- Bone health index at Final Height

Purpose of the GHD Reversal Trial

As part of the trial we will also assess a range of key secondary outcomes:

Biochemistry –

- Serum IGF-1 and lipid profiles (fasting lipids – serum triglyceride and serum total cholesterol) at Final Height
- Peak stimulated GH at Final height

Health Economics –

- Cost per percentage of children in each arm achieving Target Height
- Cost per Quality Adjusted Life Year (QALY) gained

Purpose of the GHD Reversal Trial

As part of the trial we will also assess a range of key secondary outcomes:

Qualitative Research –

- Trial acceptability to parents, patients and staff
- Parents, patients and staff reasoning for declining to participate
- Parent and patient experience of the trial and treatment pathways

Adverse Events

Trial Design, Internal Pilot & Patient Population

The GHD Reversal Trial – Trial Design

The GHD Reversal Trial is a:

- Phase III
- International
- Multicentre
- Open label
- Non-inferiority
- Randomised controlled CTIMP

Which includes:

- An internal pilot phase
- A qualitative research sub-study (UK only)
- A health economics analysis

The GHD Reversal Trial – Internal Pilot

The GHD Reversal Trial contains an internal pilot phase. This will take place during the first year of the trial and will be used to assess the trial's feasibility via the following metrics:

- Number of sites open
- GHD reversal rate
- Number of eligible patients recruited

The qualitative research sub-study will also take place during the pilot phase. As such the first 12 months of the trial are of vital importance, both in terms of the qualitative research and in terms of the overall success of the project.

The GHD Reversal Trial – Patient Population

- We are aiming to recruit 138 pubertal children into the trial
- The children will be taking growth hormone for growth deficiency
- They will be recruited from routine endocrine clinics
- Recruitment will take place in participating centres in the UK and Austria

The GHD Reversal Trial – Patient Population

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Eligibility Criteria

The GHD Reversal Trial – Eligibility Criteria

Inclusion Criteria

- Initial diagnosis of I-GHD will have been made by either two GH stimulation tests (peak GH <6.7µg/L), or one stimulation test (peak GH <6.7µg/L) with serum IGF-1 below, or in the lower tertile of, normal range for sex & age irrespective of sex-hormone priming for GH stimulation tests
- Children with reversed I-GHD (peak GH ≥6.7 µg/L using arginine or insulin tolerance test, and a serum IGF-1 within normal reference range for sex and age)
- Children with a normal brain MRI (incl. small anterior pituitary)
- Children in established puberty – Tanner stages B2/3 in girls & 6-12ml testes in boys
- Children must be within the following age ranges – 8-15 years of age (inclusive) for females and 9-17 years of age (inclusive) for males
- Children will have discontinued GH treatment for a minimum of 4 weeks prior to re-testing
- Ability to tolerate the administration of GH therapy
- Ability to comply with trial schedule and follow up
- Written informed consent obtained from patient (if over 16), or the patient's parent/guardian and written assent obtained from patient (where age appropriate).

The GHD Reversal Trial – Eligibility Criteria

Exclusion Criteria

- Multiple pituitary hormone deficiency (hypopituitarism) with or without additional pituitary hormone supplementation
- Known genetic cause of I-GHD
- Organic GHD (mid-brain tumours, congenital mid-brain malformations, septo-optic dysplasia; radiotherapy to the total body or brain)
- Ectopic posterior pituitary
- Other indications for GH therapy
- Receiving GH treatment at any time between the (minimum 4-week) GH discontinuation period and randomisation
- Receiving prednisolone or dexamethasone at any time during the (minimum 4-week) GH discontinuation period
- Known history of persistent non-compliance with prescribed medication regimens
- Pregnant or lactating
- Any malignancy
- Currently participating in another CTIMP

The Trial in Practice

The GHD Reversal Trial – In Practice

Patient Pathway – Prior to Consent

- All pre-pubertal I-GHD patients (in particular those entering puberty) should be informed about the need for early re-testing **as part of standard care**
- I-GHD patients in established puberty should be informed about the booking of a re-test
- Patients should be added to the GHD Reversal Trial Screening Log at this point
- **All I-GHD patients who will have a re-test should be informed that they will discontinue GH therapy for a minimum of 4 weeks prior to the re-test**
- As the minimum 4-week discontinuation period forms a key part of the trial's stop/go criteria, it is vital for robust screening data to be collected

The GHD Reversal Trial – In Practice

Patient Pathway – Prior to Consent

- Once the results of the re-test are available (i.e. eligible or ineligible), this should be added to the Screening Log
- The patient should then be screened against the remaining eligibility criteria
- If the patient is thought to be eligible, the trial information (GHD Reversal Trial PIS etc) can be posted out to the patient/guardian and they will be invited to clinic to discuss potentially participating in the trial
- If happy to participate, consent & randomisation can happen at this appointment

N.B. – The patient should remain off GH therapy until they attend clinic

The GHD Reversal Trial – In Practice

Patient Pathway – Prior to Consent

- You will need to keep a trial file log which links patients with their trial number (allocated post-randomisation) in the GHD Patient Recruitment and Identification Log

- You should also keep a paper Screening ID Log to ensure that patients are not screened more than once (and to facilitate updates to the GHD Reversal Trial Screening Log)

- The site team should maintain and securely store the GHD Patient Recruitment and Identification Log and Screening ID Log, which are not for submission to the Trials Office and these should be held at site in strict confidence

The GHD Reversal Trial – In Practice

Patient Pathway – Consent

- Consent will take place in person
- Site team will talk through the study with the patient and guardian (if applicable) and answer any questions they may have
- Emphasise that taking part is voluntary and the participant can withdraw at any time
- Please record whether they agree to or decline to take part in the trial on the Screening Log

The GHD Reversal Trial – In Practice

Patient Pathway – Consent

- Run through each of the statements on the consent form with the participant/guardian
  - Note that some consent items are optional, and the participant can still take part in the trial if they do not consent to those items
- Ask the participant/guardian to initial each of the boxes to show they agree with the statement
- Ask the participant/guardian to sign the form
- Ensure that the person taking consent also signs the form

The GHD Reversal Trial – In Practice

Patient Pathway – Consent

Make three copies of the form:

- Place the wet ink original in your Site File
- Put a copy in the participant's medical notes
- Give a copy to the participant/guardian
- Send a copy to the trial office at BCTU, assuming consent has been provided to do so

The GHD Reversal Trial – In Practice

Patient Pathway – Consent

Details of the informed consent discussions must be recorded in the participant's medical notes. This includes the:

- Date of discussion
- Name of the trial
- Summary of the discussion
- Version number of the PIS given to participant/guardian
- Version number of Consent Form signed
- Date consent received

The GHD Reversal Trial – In Practice

Patient Pathway – Randomisation

Once eligibility has been confirmed and informed consent has been received, the patient can be randomised into the trial. Completing the randomisation will tell you which arm of the trial the patient has been assigned to

- Randomisation will be provided by a secure online* randomisation system at BCTU
- Unique log-in usernames and passwords will be provided to site staff delegated the role of "Participant randomisation" on the delegation log
- A Randomisation form will be provided to aid with collecting data before completing the randomisation
- Patients will be randomised to either continue (GH+) their growth hormone therapy or stop (GH-) their growth hormone therapy

The GHD Reversal Trial – In Practice

Patient Pathway – Randomisation

*Randomisation will take place via paper/telephone for the start of the trial.

Unfortunately, the GHD Reversal Trial database is not yet ready. As such, we will be starting the trial using paper randomisation forms and CRFs, and to receive your participant's trial number, you will need to complete the randomisation by calling the BCTU on one of the following numbers:

Office phone: 0121 415 9131

Mobile phone, if out of office: +447584051396

The GHD Reversal Trial – In Practice

Patient Pathway – During the Trial

Once randomised, the participant will be in one of the following trial arms:

- Control Arm (GH+) – In this arm patients will (restart and) continue taking their GH medication for the duration of the trial
- Experimental Arm (GH-) – In this arm patients will (not restart) discontinue their GH medication for the duration of the trial
- All patients will be followed up at 6-monthly intervals until near FH, or until the 36 month* follow-up assessment

The GHD Reversal Trial – In Practice

Patient Pathway – During the Trial

At each patient's **baseline** visit, the following should occur:

- Recording of relevant medical history and relevant concomitant medication
- Physical examination including height, weight and Tanner stage
- Review and recording of routine re-test results
- Biochemistry – fasting lipids
- Bone age and health assessment: hand X-ray
- CHU-9D patient completed questionnaire (UK only)

Please see section 8.3 of the GHD Reversal Trial Protocol for more details

The GHD Reversal Trial – In Practice

Patient Pathway – During the Trial

At each of the patient's **6 monthly** visits, the following should occur:

- Physical examination including height, weight and Tanner stage
- Compliance check: crossover between trial arms will be monitored
    - For the GH+ arm, the percentage of treatments taken/missed will also be recorded, as a patient reported measure
- Concomitant endocrine medication related to GHD
- Adverse events
- CHU-9D patient completed questionnaire

Please see section 8.3 of the GHD Reversal Trial Protocol for more details

The GHD Reversal Trial – In Practice

Patient Pathway – During the Trial

The following procedures will be carried out at specific time-points

- If a patient within the GH- trial arm is found to have suboptimal growth and a serum IGF-1 below the normal range at the **6 month** assessment, a further GH stimulation test will be conducted to ascertain whether growth hormone therapy needs to be re-started
- Health economics data, including healthcare contacts in primary and secondary care settings, will be recorded at the **6, 12, 24 and 36 month** assessments
- Serum IGF-1 and assay used will be recorded at the **6, 12, 24 and 36 month** assessments
- Biochemistry: Fasting lipids will be measured at the **36 month** (or **near FH**) assessment
- Bone age and bone health index will be measured via a hand X-ray at the **36 month** (or **near FH**) assessment.
- A GH stimulation test will be conducted at the **36 month** (or **near FH**) assessment

Please see section 8.3 of the GHD Reversal Trial Protocol for more details

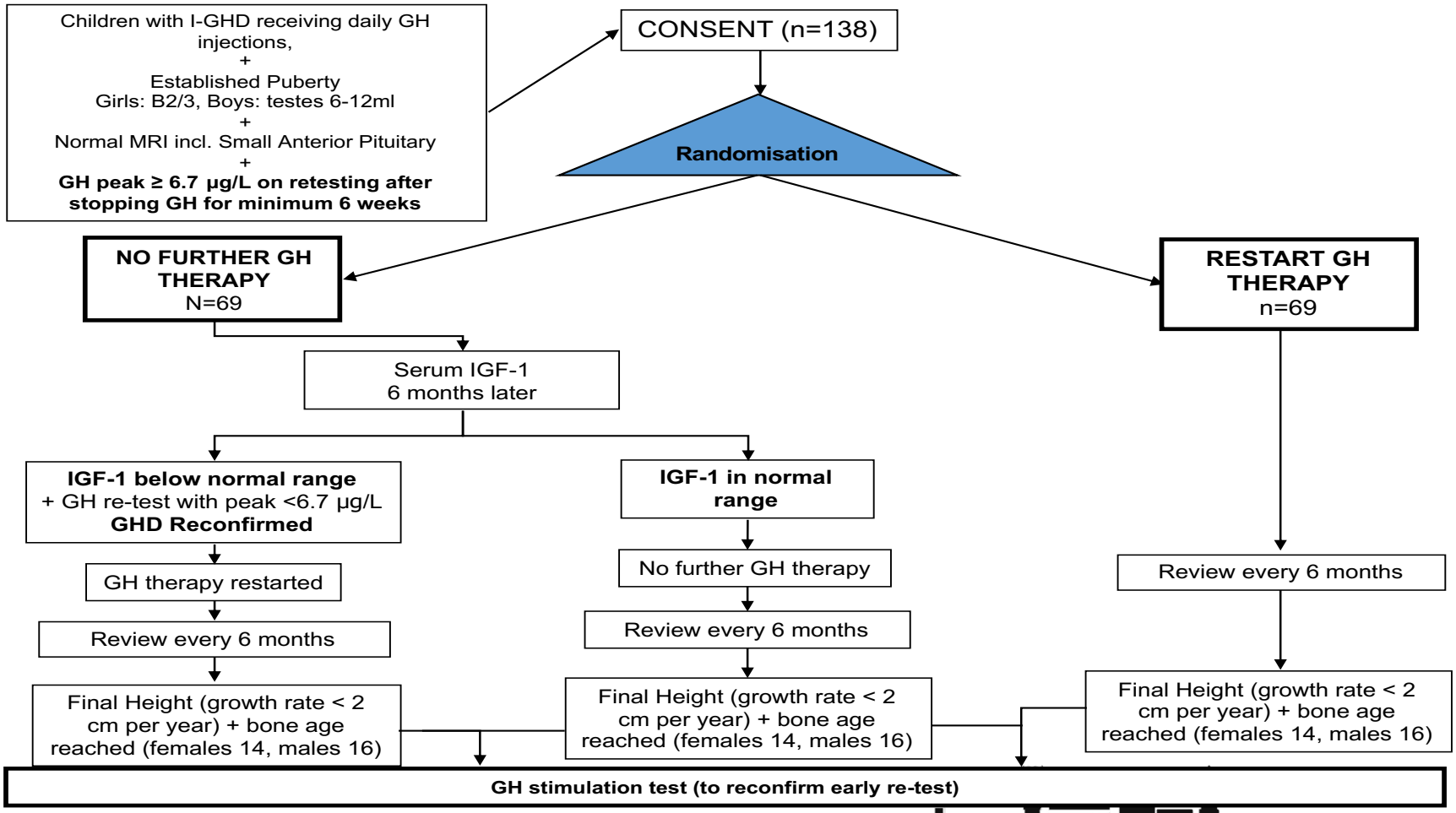
The GHD Reversal Trial – In Practice

Patient Pathway – End of the Trial

- Once near FH is reached, another growth hormone stimulation test will be performed to re-confirm the absence of GHD
- Participants in the GH+ trial arm, and any participants that have crossed over to receiving GH therapy in the GH- arm, must discontinue treatment for a minimum period of 4 weeks prior to the growth hormone stimulation test
- From this test onwards, the participant's treatment will be decided solely on clinical grounds.

The GHD Reversal Trial – In Practice

Patient Pathway – Trial Schema



Trial Setup

The GHD Reversal Trial – Trial Setup

Before starting the trial at your centre and issuing the Site Activation Letter, we need the following activities to have occurred and the following documentation in place:

- Site Initiation Visit conducted and queries resolved
- Confirmation of Capacity and Capability
- Fully signed GHD Reversal Trial Model Non-commercial Agreement
- GHD Reversal Trial Delegation log, with all duties covered
- CVs and GCP certificates for the research team
- Sponsor green light for site to open

The GHD Reversal Trial – Trial Setup

Delegation Log

- All site staff conducting activity specific to the trial need to be entered on to the GHD Reversal Trial Site Signature and Delegation Log
- Ensure that all entries on the log are signed off by the PI and person delegated the task
- If the person is assigned a randomiser role, or will be entering information directly onto the database, then we'll need their email address to issue a unique username and password to log onto the online database
- Please send an updated delegation log to BCTU whenever there are staff changes at site

The GHD Reversal Trial – Trial Setup

Site Staff CVs and GCP Certificates

We will need CVs and GCP certificates for all site staff on the delegation log

- CVs must be signed, and must be dated within a year of receipt

- GCP certificates must be valid and in-date
  - GCP certificates should be from within (at least) the last 3 years
  - If your Trust's policy is to renew GCP certificates more regularly, please conform to your Trust's policy

Investigational Medicinal Product (IMP)

The GHD Reversal Trial – IMP

The "IMP" in the GHD Reversal Trial is not really an IMP at all!

- The IMP used in the trial is for the patient's pre-existing somatropin treatment, and is to be used as per standard care, in the GH+ arm only
- Those in the GH- arm should not be taking the IMP
- As the IMP is from standard stock and is delivered as per standard care, there is no additional pharmacy involvement and no pharmacy manual
- For the GH- arm, if there is clinical indication that a participant's GH levels are no longer within the normal range at the 6 month assessment, they will restart their GH medication and this will be recorded on the GHD Reversal trial eCRFs

Monitoring and Safety Reporting

The GHD Reversal Trial – Monitoring

Monitoring of data returns, data quality and study conduct in GHD Reversal Trial will be performed centrally by the trial team at the BCTU.

If central monitoring identifies issues at specific sites (e.g. poor data returns, numerous SAEs, repeated breaches of protocol) then we will offer training for sites regarding those issues.

If the same issues persist , then on-site monitoring visits may occur.

The GHD Reversal Trial – Safety Reporting

Adverse Events

Adverse Events in the following list will be reported via GHD Reversal Trial CRFs for trial outcome analysis purposes:

- Headache
- Idiopathic intracranial hypertension
- Lipoatrophy
- Increased levels of fatigue
- Increased/unusual weight gain
- Abnormal lipid profiles

The GHD Reversal Trial – Safety Reporting

Serious Adverse Events (SAEs)

- SAEs should be recorded for all participants, from the baseline assessment until the 36 month (or near FH) assessment

- Investigators will report all SAEs that are defined in the protocol as an event which requires expedited reporting

- SAEs should be reported immediately and within 24 hours of being made aware of the event.

- All required SAEs must be collected on the GHD Reversal Trial SAE Form and noted the participant's medical notes.

The GHD Reversal Trial – Safety Reporting

Serious Adverse Events (SAEs)

- The GHD Reversal Trial SAE form should be completed and sent to the trial team at BCTU
- Relatedness and severity of the SAE will be assessed by the Principal Investigator – please see section 9.5.2 of the GHD Reversal Trial Protocol for more details
- On receipt of an SAE form, the BCTU trials team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt – ensure the reference number is used in all correspondence regarding the SAE
- Where an SAE Form has been completed by someone other than the Investigator, the original SAE form is required to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.
- Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event
- Any follow-up information will be requested by the BCTU trials team via a Data Clarification Form (DCF), using the SAE reference number provided by the BCTU trials team

End of the Trial

The GHD Reversal Trial – End of Trial

Prior to Database Lock

The PI (or their delegate) will be sent an independent copy of their data (i.e. that which has originated from within the Trust)

The PI (or their delegate) will be asked to acknowledge receipt of this independent copy of their data, and let us know of any CRFs that are still outstanding, or if there are any queries about the dataset

The PI (or delegate) does not have to confirm accuracy of the data as these checks should have occurred as the data was being entered

After confirmation of receipt of the independent copy of their data the database can be locked – the PI (or their delegate) will still have read only access to 'their' data

Archiving

The GHD Reversal Trial – Archiving

It is the responsibility of the PI* to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISFs, participants' hospital notes, CRFs etc.) at their site are securely retained for at least 25 years

Archiving will be authorised by UCL and UoB at the end of trial following submission of the Clinical Trial Summary Report

No documents should be destroyed without prior approval from the Sponsor and the authorised person within the University of Birmingham

*Can be devolved to your R&D Department

Thank you for your time