The GHD Reversal Trial Protocol

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

This protocol has regard for the HRA guidance

Version Number: Version 4.0

Version Date: 23rd Janurary 2024

Protocol development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**
Amendment 01 (NSA1)	30-May-2022	2.0	Non-substantial	Inclusion of specified age range within eligibility criteria
Amendment 03 (SA1)	11-Aug-2023	3.0	Substantial	Eligibility criteria widened, update to trial RSI, introduction of potential PIC sites
Amendment 04 (SA2)	23-January-2024	4.0	Non-substantial	Update to eligibility criteria to allow glucagon as a stimulation test and specification of height measurement process

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Protocol Sign Off

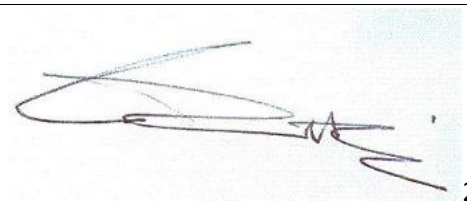
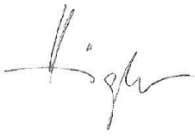
CI Signature Page

The undersigned confirms that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

This protocol has been approved by:

Trial Name: Protocol Version Number: Protocol Version Date:	NIHR127468 - The GHD Reversal Trial Version: 4.0 23rd January 2024
CI Name:	Professor Mehul Tulsidas Dattani
Trial Role:	Chief Investigator
Signature and date: National Coordinator for Austria	 24 January 2024 Professor Wolfgang Högler
Signature and date:	 23. Jan 2024

Sponsor Statement:

By signing the IRAS form for this trial, University College London, acting as sponsor of this trial, confirm approval of this protocol.

Compliance Statement:

This protocol describes the GHD Reversal trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the GHD Reversal trial.

The trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive and laid down in UK law by the Medicines for Human Use (Clinical Trials) Regulations (2004) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

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PI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	NIHR127468 – The GHD Reversal Trial
Protocol Version Number:	Version: 4.0
Protocol Version Date:	23rd January 2024
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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
APR	Annual Progress Report
BASG	Bundesamt für Sicherheit im Gesundheitswesen
BCTU	Birmingham Clinical Trials Unit
BNFc	British National Formulary for Children
CI/Co-CI	Chief Investigator/Co-Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DCF	Data Clarification Form
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FH	Final adult Height
FH SDS	Final Height Standard Deviation Score
GOSH	Great Ormond Street Hospital
GH	Growth Hormone
GH+	Continue growth hormone therapy
GH-	Discontinue growth hormone therapy
GHD	Growth Hormone Deficiency
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
I-GHD	Isolated Growth Hormone Deficiency
ICF	Informed Consent Form
IGF-1	Insulin-like Growth Factor 1
ISF	Investigator Site File
ITT	Intention to Treat
JKU	Johannes Kepler Universität
LOCF	Last Observation Carried Forward
MRI	Magnetic Resonance Imaging
NEJM	New England Journal of Medicine

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAGhE	Safety and Appropriateness of Growth hormone treatments in Europe
SAR	Serious Adverse Reaction
SDS	Standard Deviation Score
SUSAR	Suspected Unexpected Serious Adverse Reaction
TH	Mid-parental Target Height
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
UoB	University of Birmingham
UCL	University College London

TRIAL SUMMARY

Title: The GHD 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.

Aims:

1) To assess whether children with early Growth Hormone Deficiency (GHD) reversal who stop growth hormone therapy (GH-) achieve no worse near Final Height Standard Deviation Scores (FH SDS) (primary outcome), Target Height (TH) minus near Final Height (FH), Health Related Quality of Life (HRQoL), bone health index and lipid profiles (secondary outcomes) than those continuing growth hormone (GH+).

2) To determine the cost-effectiveness of GH- in the early re-testing scenario, and the cost-effectiveness of the new care pathway (early re-testing) compared to traditional care (late re-testing).

3) To assess staff, parent and patient perspectives of the trial pathways and reasons for declining to participate or dropping-out of the trial.

Objectives:

1) To compare near Final Height Standard Deviation Score (FH SDS) in the GH+ and GH- groups, Mid-parental Target Height (TH) (estimated from parental heights[1]), and TH-FH (in cm and SDS from FH reference data[2]).

2) To compare the lipid profiles (fasting lipids - serum triglyceride and serum total cholesterol) and bone health in the GH+ and GH- groups.

3) In an internal pilot, to record re-testing, GHD reversal, and recruitment rates.

4) To undertake qualitative research to explore staff, parent and patients' perspectives regarding the trial and treatment pathways, including obtaining views regarding the recruitment process, reasons for declining participation and experience of the treatment pathways.

5) Undertake a trial-based economic evaluation to determine the cost-effectiveness of Growth Hormone (GH) discontinuation in the early re-testing scenario by estimating the cost per percentage of children achieving their sex-specific, mid-parental TH range (lower end of 95% CI), and the difference in HRQoL as measured using Quality-Adjusted Life Years (QALYs), between the GH- and GH+ groups. In addition, the cost-effectiveness of the new care pathway (early re-testing) will be compared to traditional care (late re-testing) using a decision modelling approach.

Trial Design:

Phase III, multicentre, open-label, randomised controlled non-inferiority trial including an internal pilot study, qualitative sub-study and within-trial cost-effectiveness analysis.

Participant Population and Sample Size:

138 pubertal children taking growth hormone for growth deficiency recruited from routine endocrine clinics in participating centres in the UK (12) and Austria (5).

Trial Duration and Timeline

The duration of the trial will be 90 months, including a 12 month pilot phase.

Trial setup will take place during months 1-6. Months 7-84 will comprise of patient recruitment and follow up. Recruitment will take place between months 7 and 48 (including a 12 month pilot phase). Patient follow up will take place between months 7 and 84. Months 85-90 will comprise of final data gathering and cleaning, data analysis, and report preparation.

Eligibility Criteria:

Inclusion criteria

Children (8-15 years of age for girls, 9-17 years of age for boys) with reversed Isolated Growth Hormone Deficiency (I-GHD) in established puberty (Tanner stages B2/3 in girls & 6-12ml testes in boys) and normal brain Magnetic Resonance Imaging (MRI) scan result (incl. small anterior pituitary). Children will need to have completed a minimum 4-week period of discontinuation of GH medication prior to a GH re-test. Children demonstrating GHD reversal (defined as a peak stimulated GH equal to or greater than 6.7 µg/L using glucagon, arginine, or insulin tolerance test) will be eligible to participate in this trial. Written informed consent must be obtained.

Exclusion criteria:

Hypopituitarism with or without additional pituitary hormone supplementation, a known genetic cause for I-GHD, organic GHD, ectopic posterior pituitary, other indications for GH therapy, pregnancy or lactation, any malignancy, current participation in another CTIMP, receipt of prednisolone or dexamethasone during the (minimum) 4-week discontinuation period before GH re-test.

Intervention:

Stopping GH therapy (GH-) versus continuation of GH therapy (GH+).

Outcome Measures:

Primary Outcome:

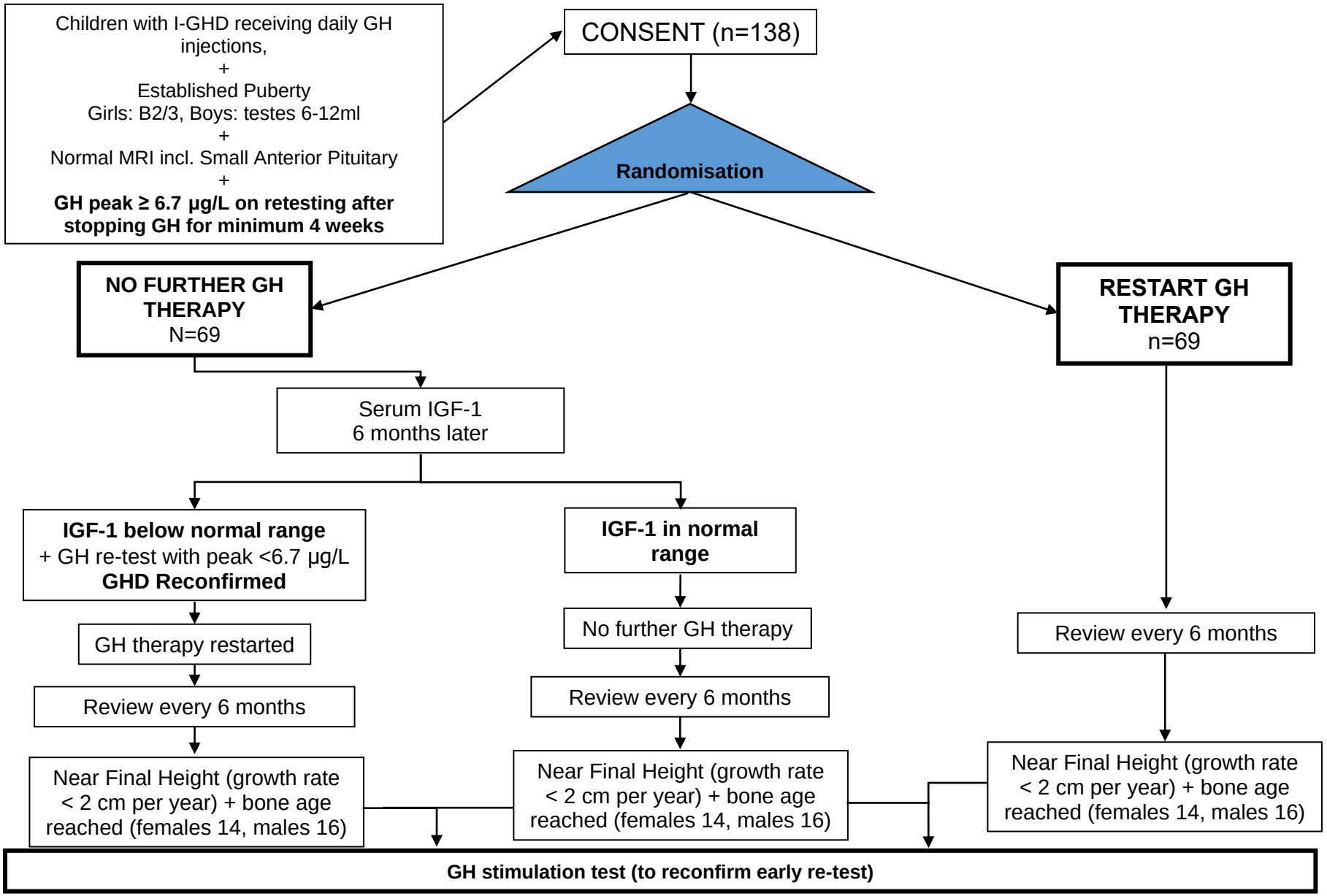
- Near Final Height in Standard Deviation Score

Secondary Outcomes:

- Growth-related:
    - The proportion of children reaching normal adult height[3] (0 +/- 2SD)
    - The proportion of children reaching mid-parental Target Height (0 +/- 2SD)
    - Difference in Target Height minus near Final Height (in Standard Deviation Score and centimetres) between GH+ and GH- groups
- Bone-related:
    - Bone age delay at near Final Height
    - Bone age acceleration between enrolment and near Final Height
    - Bone health index at near Final Height
- Biochemistry:
    - Serum IGF-1 and lipid profiles (fasting lipids - serum triglyceride and serum total cholesterol) at near Final Height
    - Peak stimulated GH at near Final Height
- Adverse events
- Health Economics:
    - Cost per percentage of children in each arm achieving Target Height
    - Cost per Quality Adjusted Life Year (QALY) gained
- Qualitative Research

- Trial acceptability (parents, patients and staff); reasons to decline the trial; parent and patient experience of the trial and treatment pathways

Trial Schema



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1. BACKGROUND AND RATIONALE

1.1. Background

Around 500 children are diagnosed with growth hormone deficiency (GHD) every year in the UK, of whom 75% have idiopathic, isolated GHD (I-GHD)[4]. Children are treated with daily growth hormone (GH) injections until final height (FH) is reached, at an annual cost of £10,000 - £23,000 per child[5]. However, when these children are re-tested after having reached their full height, between 26-88% of them are found to be producing sufficient endogenous GH not to have required the therapeutic intervention[6-18], i.e. their GHD has reversed. Children with a normal pituitary on brain MRI and partial GHD are more likely to reverse. However, it is not unknown for children with structural abnormalities of the pituitary gland to also reverse[12, 14]. The underlying reasons for this reversal are largely unknown but may be explained by 1) late maturation of the GH axis, or 2) difficulties inherent in the original diagnostic process.

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 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 [formerly 10mU/L][19]. However, a number of GH stimulation tests are used in routine practice and there is no consensus as to which is optimal for either diagnosing GHD or predicting a later GHD reversal[20]. Diagnostic test protocols also vary between institutions.

Growth hormone deficiency (GHD) occurs when the pituitary gland does not produce enough human growth hormone (HGH) and is the commonest hormonal cause of short stature. GHD may occur as an isolated deficiency (I-GHD) or in combination with deficiencies in several pituitary hormones (hypopituitarism). It is estimated that approximately 175-200 children born each year in the UK will develop GHD[21, 22].

GH treatment allows children with GHD to develop normally. Parents of children with short stature usually consult an endocrinologist because of concerns that their child may be disadvantaged as an adult. Once other conditions are ruled out, and the diagnosis of "isolated GHD (I-GHD)" is made, a brain MRI scan is usually performed to exclude structural abnormalities. In most cases, the pituitary gland is normal or the anterior pituitary is considered slightly small for a child of that age. In this common scenario, in conjunction with a GH stimulation test confirming that the patient has GHD, the clinician starts GH therapy administered as daily injections that are continued until the child reaches their final/adult height (FH - defined as growth velocity less than 2 cm/year).

Although I-GHD is known to reverse in many children, current practice is to continue treatment with daily injections of GH until FH is achieved. These injections are 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.

A number of studies have shown that sex steroid priming improves the response to provocative testing[23-25]. Additionally, studies have shown that the peak GH response is inversely correlated to weight within a cohort of normal weight children[26]. Given all of these variables, it may not be surprising that the GH stimulation test itself could be associated with a high false positive rate, and that re-testing after a suitable period, or at the end of GH treatment, may produce normal results, implying a reversal of GHD.

A further GH stimulation test (re-test) is usually performed when FH is attained to assess any requirement for adult GH therapy, and it is at this point that many patients are found to

be no longer GH deficient. However, five previous studies have demonstrated reversal of GHD (mean 49%; range 19-95%) with earlier re-testing, before or during puberty[6-8, 17, 18]. One study found that children with GHD reversal confirmed during puberty reach their target height (TH) without further GH therapy[8]. Another study showed that children stopping GH 1.6 years before attaining FH achieve a similar FH to those who continue taking GH until they reach their FH[27]. Hence, establishing normal GH status in early puberty would relieve patients from the diagnostic uncertainty of GHD persistence and may allow patients to stop GH therapy earlier whilst still reaching a normal FH, relieving them of the burden of daily injections of an unnecessary medication, and at a considerably reduced cost to the NHS[5].

It is important to note that GH treatment is not without its problems. Previous studies have suggested rare side-effects including benign intracranial hypertension, diabetes and slipped femoral capital epiphysis in association with GH treatment[28]. Other studies have suggested a higher incidence of bone tumours[29] in patients with normal endogenous GH secretion who were treated with high doses of GH. The SAGhE study has suggested there may be an increased incidence of cerebrovascular events in people who previously received GH treatment[30]. However, more recently, detailed registry reviews indicated no increased risk of strokes or cancer once known risk factors had been accounted for[31]. Nonetheless, some controversy remains around safety of GH therapy, and it is important to ensure that GH is only considered in those patients who would benefit from its use. This randomised, controlled, non-inferiority trial will assess the safety, efficacy, health-related quality of life, cost effectiveness, biochemical and bone health effects of discontinuing GH therapy in children who have a normal GH re-test in established puberty. The acceptability of the trial and treatment pathways to patients, parents and staff will be explored via a qualitative research sub-study.

This trial will recruit 138 children with I-GHD whose deficiency has reversed on re-testing during early puberty. Following consent, children will be randomised to either continue or discontinue GH therapy. The trial will test whether the FH of those stopping GH treatment is not inferior to the FH of those continuing treatment. The centres taking part in this trial routinely perform a GH re-test in early puberty (approximately 3 years before FH is reached).

If this trial shows that a significant proportion of children with I-GHD generate sufficient endogenous GH in early puberty to reach a FH within the target range, then this new care pathway would rapidly improve practice, free children from the burden of daily injections and the unnecessary exposure to potentially significant side effects, as well as providing substantial savings for health care systems.

1.2. Trial Rationale

1.2.1. Justification for participant population

Benefit for patients and the NHS

Identifying children at puberty who have reversed GHD and halting administration of unnecessary growth hormone may give them and their carers diagnostic certainty and liberate them from daily injections, blood tests, X-rays, and clinic, pharmacy and GP visits. Additionally, earlier re-testing may prevent any harmful adverse effects of GH therapy.

The risk to reversed children of stopping administration of additional GH is likely to be minimal, since they are now producing sufficient endogenous GH[32]. Additionally, within-trial testing will be conducted to detect any re-emerging GHD.

If successful, the GHD trial may benefit the NHS by freeing resources such as clinic space, and may lead to financial benefits.

Families and carers of children with short stature are often concerned that their child's short stature may disadvantage them in later life, and limited evidence supports this concern ([33-35]. Health-related Quality of Life (HRQoL) may be reduced in I-GHD children[35], but evidence suggests that HRQoL is not reduced for adults that have previously been treated for I-GHD[33, 34]. Increments in growth rate and height resulting from GH treatment have not predictably improved psychosocial well-being, even when the surrogate measure of FH was increased[5, 33, 34]. While GH treatment improves or accelerates FH achievement in I-GHD, evidence of the long-term impact of short stature or GHD on HRQoL and therapy adherence in adolescence[36] remains limited.

1.2.2. Justification for design

The mechanism underlying GHD reversal remains unclear. One theory suggests that the increase in sex hormone concentrations in puberty causes late maturation of the GH/IGF-1 axis, whilst another raises the possibility of inaccuracy in the stimulation test used to detect GHD ("overdiagnosis")[37]. Part of this test inaccuracy is revealed by sex hormone priming before testing, which is known to increase GH responsiveness. Additionally, a possible change in body mass index post-puberty may impact on the peak GH in response to stimulation. Potentially, GH stimulation test results pre-pubertally may simply be physiologically lower than those at the time of re-testing. High "re-test normal" rates at FH (26-88%) are common in I-GHD patients with normal brain MRI, or pituitary hypoplasia, the large variation being explained by different patient populations and peak GH cut-offs used[6-16].

The lack of sex hormone priming of GH stimulation tests may also give a higher false positive rate for GHD on initial testing, with restoration of normal GH secretion at the time of re-testing. A recent audit at Birmingham Children's Hospital identified that I-GHD reversed in 54% of subjects (n=55; cut-off 5 µg/L) following pre-priming with sex hormones. To date, five studies[6-8, 17, 18] have demonstrated I-GHD reversal in 161 of a combined total of 326 subjects (reversal rate 49%; range 19-95%) at early re-testing either before or during puberty. Only one of these studies assessed FH outcomes of reversed patients. Zucchini *et al* [8] re-tested 69 pubertal children and showed that GH discontinuation in the 25 children with GHD reversal was safe and FH was only approximately 0.3 cm (girls) and 0.9 cm (boys) lower than in children with GHD persistence, a clinically insignificant difference. However, diagnostic criteria for GHD have been revised since these studies, and the peak GH production to diagnose GHD lowered from 10 to 6.7µg/L[19]. Various GH cut-offs (6-7µg/L) are used in the UK and elsewhere[38]. Given the arbitrary nature of the diagnostic peak GH cut-off, agreement was reached among our centres to regard a peak GH ≥6.7µg/L as normal. The GHD reversal rate on the new diagnostic criteria and the number of reversed children reaching TH without further GH therapy is unknown.

In support of the study by Zucchini *et al* [8] a large retrospective study[27] of 2852 I-GHD children, reported similar FHs in those discontinuing GH therapy an average of 1.6y earlier to those continuing GH until FH (expressed as standard deviation score (SDS, or z-score) -1.5, [n=933] vs -1.6 [n=1232], respectively).

1.2.3. Choice of intervention

Established practice is to administer GH therapy in children with I-GHD until FH is achieved, despite emerging evidence that GHD reversal is common. Whilst this treatment is necessary in children with true, organic GHD or hypopituitarism the requirement of this practice in children with reversible I-GHD is an important question.

To date, there is little evidence for detrimental psychological outcome or reduced HRQoL in adults with short stature[33, 34]. Nonetheless, children with short stature may have a reduced HRQoL[35], and we will explore this outcome during the course of this trial.

GH has direct, anabolic effects on muscle and bone[39], so the safety of GH discontinuation on bone health will be studied as a secondary outcome by centrally analysing radiographs of the non-dominant hand using specialised software (BoneXpert). The X-ray analysis via BoneXpert will also be used to provide a measure of skeletal growth (i.e. bone age), which forms part of the criteria for confirmation of near FH in this trial.

Adults with untreated GHD may have an adverse metabolic profile and increase in atherogenic factors, with reduced insulin sensitivity, increased proinflammatory markers, unfavourable lipid profiles, and changes in coagulation with increase in fibrinogen and active plasminogen activator inhibitor type 1 (aPAI-1), all contributing to impairment of endothelial and cardiovascular function[40, 41]. In adolescents with GHD, the discontinuation of treatment at completion of linear growth may be associated with adverse effects on body composition, lipid profile, and cardiac morphology, which is now reflected in consensus guidelines on recommendation for GH treatment in transition[40, 41]. We will therefore monitor blood lipid profiles (fasting lipids - serum triglyceride and total serum cholesterol) in recruited patients by testing at enrolment and near FH.

If this trial shows that children with early I-GHD reversal and subsequent GH discontinuation have no clinically meaningful deficit in near FH, HRQoL, lipid profiles (fasting lipids - serum triglyceride and total serum cholesterol) or bone health, and remain GH sufficient at near FH, then it will help inform a new, evidence-based care pathway, and significantly alter the practice of paediatric endocrinology.

2. AIMS AND OBJECTIVES

2.1. Aims

1) To assess whether children with early Growth Hormone Deficiency reversal who stop growth hormone therapy (GH-) achieve no worse; near Final Height Standard Deviation Scores (FH SDS) (primary outcome), Target Height (TH) minus near Final Height (FH), Health Related Quality of Life (HRQoL), bone health index and lipid profiles (secondary outcomes) than those continuing growth hormone (GH+).

2) To determine the cost-effectiveness of GH- in the early re-testing scenario, and the cost-effectiveness of the new care pathway (early re-testing) compared to traditional care (late re-testing).

3) To assess staff, parent and patient perspectives of the trial pathways and reasons for declining to participate or dropping-out of the trial.

2.2. Objectives

1) To compare near Final Height Standard Deviation Score (FH SDS) in the GH+ and GH- groups, Mid-parental Target Height (TH) (estimated from parental heights[1]), TH-FH (in cm and SDS from FH reference data[2]).

2) To compare the lipid profiles (fasting lipids - serum triglyceride and total serum cholesterol) and bone health in the GH+ and GH- groups.

3) In an internal pilot, to record re-testing, reversal and recruitment rates.

4) To undertake qualitative research to explore staff, parent and patients' perspectives regarding the trial and treatment pathways, including obtaining views regarding the recruitment process, reasons for declining participation and experience of the treatment pathways.

5) Undertake a trial-based economic evaluation to determine the cost-effectiveness of Growth Hormone (GH) discontinuation in the early re-testing scenario by estimating the cost per percentage of children achieving their sex-specific, mid-parental TH range (lower end of 95% CI), and the difference in HRQoL as measured using Quality-Adjusted Life Years (QALYs), between the GH- and GH+ groups. In addition, the cost-effectiveness of the new care pathway (early re-testing) will be compared to traditional care (late re-testing) using a decision modelling approach.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

Phase III, multicentre, open-label, randomised controlled non-inferiority trial, including an internal pilot study, qualitative sub-study and within-trial cost analysis.

3.2. Trial Setting

The trial will take place in paediatric endocrine centres in the UK and Austria. Children will be recruited from routine endocrine clinics in participating centres.

3.3. Sub-studies

Health Economics

A health economic analysis will be conducted in UK patients to determine the cost-effectiveness of GH discontinuation in the early re-testing scenario in an NHS setting by estimating the cost per percentage of children achieving TH of GH- compared to GH+, and the cost-effectiveness of the new care pathway (early re-testing) compared to traditional care (late re-testing).

Qualitative Research

We will conduct qualitative research with UK carers, children and staff participating in the internal pilot study. The main aim of the qualitative research is to ensure the feasibility and acceptability of the trial for patients, carers and clinicians, with a particular focus on recruitment processes. These data will provide useful insights into carers' and children's preferences for treatment and help optimise the main trial processes. This research will explore carers' and children's perceptions in relation to re-testing normal (i.e. GHD reversal), reasons for agreeing to or declining trial participation, reactions to treatment allocation and associated recruitment and retention during the internal pilot. The qualitative research team will work closely with the recruiting sites and Trial Management Group (TMG) during the internal pilot to facilitate recruitment.

Data collection will include audio-recordings of recruitment consultations and interviews with carers, children and staff.

We will consent staff at UK recruiting sites, and potential trial participants (children and carers) to audio-record recruitment consultations. Recording recruitment consultations will provide valuable data concerning how the trial and treatment groups are presented by staff and how this is received by potential participants and their carers. Following consent, semi-structured interviews will be conducted with a sample of carers and children participating in both arms of the pilot study (n≈20-24), as well as carers and patients who decline to take part in the trial (n≈8-10). We will undertake interviews with site PIs and staff who are recruiting patients to the trial. These interviews will take place early in the pilot phase at all UK sites that are open to recruitment so that we can understand their perspectives on the trial and the GHD re-testing pathway, and understand early experiences and perspectives regarding recruitment to the trial. It is likely that the majority of interviews will take place remotely (e.g. telephone) but we will explore the possibility of face-to-face interviews where logistics (e.g. geography,) allow.

Children recruited to the pilot and their carers will be interviewed at two time points: T1 – approximately 2 weeks after randomisation; and T2 – approximately 6 months following randomisation. Where possible interviews will be conducted at a time and place preferred by participants, either in person or remotely e.g. over the telephone. Separate interviews will be conducted with the carers and the children themselves, unless children wish to be interviewed whilst their carers are present.

T1 and decliner interviews will focus on the recruitment process, children's motivations for taking part or not in the trial, and specific barriers and facilitators to patient participation. In addition, T1 and decliner interviews will also explore children's and carers' experiences of GHD and its impact on their daily lives, their understanding and expectations of GHD testing and treatment options, and their expectations for the trial. T2 interviews will explore children's and their carers' experience of the trial and treatment options, and of related trial processes and procedures.

Data collection and analysis will proceed iteratively until the research team judge that the data and sample size have sufficient depth and breadth[42]. Analysis of audio-recordings will target key components of discussions regarding trial participation using thematic and conversation analysis techniques[43] A thematic analysis of interview content will be informed by the Framework analytical approach[44]. Following initial familiarisation with the interview data, development of thematic frameworks and data coding will proceed in an iterative manner within the qualitative research team. Data collection and analysis will run concurrently so that emergent analytical themes can inform further data collection. Data will be managed using QSR NVivo version 12 (or higher as/when updated versions are available).

3.4. Assessment of Risk

All clinical trials can be considered to involve an element of risk and, in accordance with BCTU operating procedures this trial has been risk assessed, to clarify any risks relating uniquely to this trial. This risk assessment undertaken in conjunction with the CI and lead clinician concluded that the GHD Reversal Trial should be categorised as:

Type A = No higher than the risk of standard medical care.

4. ELIGIBILITY

4.1. 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 glucagon, 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 (as measured by orchidometer**)
- 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 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.

4.2. 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 Clinical Trial of an Investigational Medicinal Product (CTIMP)

4.3. Pregnancy and Birth Control

There is no identified risk of congenital anomalies or birth defects in the offspring of patients associated with GH therapy. Furthermore, no harm has been reported in female patients if pregnancy occurs whilst receiving treatment, and GH therapy is not routinely discontinued if a patient falls pregnant. Specific contraceptive advice whilst on GH therapy is not given within routine clinical practice, and so recommendations for appropriate contraception methods will not be included as part of the GHD Reversal Trial.

As part of the trial safety reporting procedures, female participants will be screened, following their local hospital's usual practice, for pregnancy at each follow up assessment, and any pregnancy should be reported in line with the protocol.

5. CONSENT

5.1. Pre-Consent

All pre-pubertal patients with I-GHD in routine endocrine clinics, in particular those entering puberty, are informed of the need for routine early re-testing. Patients seen in routine clinics in established puberty are informed about the booking of a routine re-test (to be conducted on a ward or in day care) and screening for the trial. Administration of GH will be discontinued for a minimum of 4 weeks prior to the re-test, as part of standard care. This should be documented in the patient's medical notes and at this point patients should be added to the GHD Reversal Trial Screening Log.

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. Once patients have taken their GH re-test (glucagon, arginine or insulin tolerance test), following the minimum 4-week discontinuation period, the patient's entry on the GHD Reversal Trial Screening Log should be updated with the result of their GH re-test (i.e. eligible or ineligible). The GHD Reversal Trial Screening Log must not contain any patient identifiable information. Sites should maintain a separate document to enable the correct patient's record on the GHD Reversal Trial Screening Log to be updated. This document must be kept completely confidential, must remain at site at all times and is not for submission to the trial office.

Once the result of the GH re-test is available (and establishes that the patient has GHD reversal), the patient will be screened against all other eligibility criteria, and the GHD Reversal Trial Screening Log can be updated further. If the patient is thought to be eligible, the GHD Reversal Trial Parent/Guardian and Participant Information Sheets (PIS) can be posted to the patient/parent/guardian (alongside the GHD Reversal Trial Letter to Accompany PIS) by their clinical team, and the patient and parent/guardian will be invited to clinic to discuss the results and potential participation in the trial. If happy to proceed, the patient can be consented and randomised at this appointment. The patient should remain off GH therapy until they attend clinic.

Investigators or delegate(s) will ensure that they adequately explain the aims, trial interventions (i.e. experimental vs control), anticipated benefits and potential hazards of taking part in the trial to the potential participant and parent/guardian. They will also stress that participation is voluntary and that the participant or parent/guardian is free to refuse to take part and may withdraw from the trial at any time without giving a reason why and the care of the child will not be affected. The potential participant and parent/guardian will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The potential participant and parent/guardian will be given the opportunity to ask any questions and have them answered in a way they understand, before they begin the consent process.

5.2. Consent

It will be the responsibility of the Principal Investigator (PI) or their delegate to ensure written informed consent is obtained for each participant and/or parent/guardian prior to performing any trial related procedures. The responsibility for obtaining consent may be delegated by the PI to another clinician or other suitably trained member of the research team as captured on the GHD Reversal Trial Site Signature and Delegation Log, but the PI

must ensure that this has occurred prior to any trial related procedures being performed on the participant.

If the potential participant and/or parent/guardian are willing to take part in the trial (and meet all of the eligibility criteria) they will be asked to sign and date the latest version of the GHD Reversal Trial Informed Consent Form (ICF) and Assent Form if appropriate. The participant and/or parent/guardian will give explicit consent for the regulatory authorities, members of the research team and or representatives of the Sponsor to be given direct access to the participant's medical records as required. This will be specified on the ICF.

The PI or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant and/or parent/guardian, a copy will be filed in the medical notes, and the original placed in the GHD Reversal Trial Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF and recorded in the participant's medical notes. A copy of the signed ICF will be sent to the Birmingham Clinical Trials Unit (BCTU) trials team for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to the participant and parent/guardian, version number of ICF signed, the date consent was received, and that the person signing the consent form on behalf of the child has been determined to have the parental or legal responsibility to do so. If a translator has been used this should be noted in the patient medical records. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

If the participant reaches 16 years of age during their trial follow-up they will be asked to re-consent using the GHD Reversal Trial Young Person (16-18 years) ICF in association with the GHD Reversal Trial Young Person (16-18 years) PIS. This process should be recorded in the participant's medical notes. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). In addition, a copy of the signed ICF will be sent to the Trials Office.

At each visit the participant and/or parent/guardian's willingness to continue in the trial should be ascertained and documented in the medical notes and on the Case Report Form (CRF). Throughout the trial the participant and/or parent/guardian will have the opportunity to ask questions about the trial and have them answered to their satisfaction.

Where new information becomes available which may affect the participant's and/or parent/guardian's decision to continue, this will be provided to the participant and parent/guardian and they will be given time to consider the information. If the participant and/or parent/guardian are happy to continue, they will be re-consented. Re-consent will be documented in the medical notes. The participant's and/or parent/guardian's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trials Office and the trial website (www.birmingham.ac.uk/GHD) and for UK sites will be printed or photocopied onto the headed paper of the local institution. With the participant's and/or parent/guardian's prior consent, the participant's General Practitioner (GP) or community paediatrician will be informed that they are taking part in the trial.

Qualitative Research Consent

We will consent staff at UK recruiting sites, and potential trial participants (children and carers) to audio-record recruitment consultations. Staff discussing the trial with parents and patients will take consent/assent to audio-record their discussions with carers and children.

Participant Information Sheets PIS(s) will be sent to potential trial participants in advance of consultations at which the trial will be discussed. Prior to the consultation the clinician will check participant(s) have received and read the relevant PIS(s), and ask if they wish to participate in this element of the qualitative sub-study. They will give participants the opportunity to ask questions and seek any clarifications. The clinician, or other suitably trained member of the research team will then take written consent and/or assent for audio-recording the consultation. This will also include consent/assent for being contacted by the qualitative research fellow about subsequent participation in the qualitative interviews. Participants may take part in the qualitative interviews, even if they did not consent for their recruitment consultation to be recorded.

Participants who express an interest in taking part in the qualitative interviews will be asked to fill in a 'contact details' form by the clinician. Consent/assent and contact details forms will then be sent to the qualitative research team at the University of Birmingham. The qualitative researcher will then contact the participant(s) *via* their preferred method, as specified on the contact details form to send out the interview PIS. No sooner than 48 hours later, the qualitative researcher will contact the participant(s) to answer any questions they may have and potentially arrange a time/date for the qualitative interview to take place.

The majority of interviews will be conducted remotely, via telephone or live video calling, using online video software. Therefore, participant informed consent and/or assent will be provided verbally and recorded on an audio file. To ensure process standardisation, the process outlined below will be followed whether interviews are conducted remotely, or face-to-face. Prior to the beginning of the interview the researcher will ask participant(s) about their understanding of the qualitative sub-study and the interview focused PIS, to ensure any consent and/or assent given is fully informed. Further, participants will be given the opportunity to ask questions, and seek clarification on any aspects of the qualitative research. Once the researcher is satisfied that all research processes are fully understood, they will begin audio recording consent and/or assent on a Dictaphone. This recording will be produced on a separate file to the interview to avoid the consent and/or assent process being shared with the transcription service provider. The researcher will read out each statement on the appropriate consent and/or assent form and produce a written record of the answers given by the participant(s) on a consent and/or assent form, on their behalf. A copy of the written record will be provided to the participant(s). Should the participant(s) not consent or assent to an aspect of the qualitative interview process, as indicated by a refusal to agree to a related statement on the form, the interview process will be terminated.

6. RECRUITMENT, ENROLMENT AND RANDOMISATION

6.1. Screening, Enrolment & Recruitment

All children with I-GHD under the care of a paediatric endocrinologist and/or a general paediatrician, should be reviewed at least once every 6 months in a hospital out-patient setting. Potential subjects will be identified at the time of their routine clinic attendance, or by members of their clinical team via hospital databases in between their routine clinic appointments. Potentially eligible patients may also be identified at Participant Identification Centres, and then referred to the relevant participating centres for recruitment.

Patients seen in routine clinics in established puberty should be informed about the booking of a routine re-test of their growth hormone levels as per local practice. In order to monitor the GHD reversal rate (as required for the trial's Stop/Go criteria) the result of this re-test will be captured on the GHD Reversal Trial Screening Log as part of screening data. All eligibility criteria can be added to the GHD Reversal Trial Screening Log in an "eligible" or "ineligible" format, to allow accurate recording of screening data. Using this "eligible" or "ineligible" format should provide robust data for the trial's Stop/Go criteria.

Administration of GH medication will be stopped for a minimum of 4 weeks prior to a GH re-test being performed in line with local protocols. After re-testing, the child and their carers will be seen in clinic where, if eligible, their willingness to participate in the study will be investigated. If the child and their carer have any questions and these are answered to their satisfaction, and both agree to participate, then informed consent/assent will be taken and the child will be randomised to one of the study arms.

Investigators will keep their own trial file log which links patients with their trial number (allocated post-randomisation) in the GHD Participant Recruitment and Identification Log. Investigators should also keep a paper Screening ID Log to ensure that patients are not screened more than once and to allow updates to the GHD Reversal Trial Screening Log. The Investigator must maintain and securely store the GHD Participant 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.

As noted above, once the result of the GH re-test is available (and establishes that the patient has GHD reversal), the GHD Reversal Trial Parent/Guardian and Participant Information Sheets (PIS) can be posted to patients/parents/guardians by their clinical team.

Prior to randomisation, eligibility will be confirmed by the PI or an appropriately medically qualified individual. Any individual that confirms a patient's eligibility for the trial must have the appropriate duty assigned to them on the GHD Reversal Trial Signature and Delegation Log and this must be signed off by the PI.

At their clinic appointment, the potential participant will be approached by an appropriately trained member of the clinical team who has been delegated this task on the site delegation log, regarding entering the GHD Reversal Trial. This individual will discuss the trial with the patient/parents/guardians in detail (informing them of any possible benefits or risks relating to participation) and will also satisfactorily answer any questions that the child and/or their carers may have regarding the trial. After allowing sufficient time for the child and their carers to consider participation, written, informed consent (or assent depending on age) will

then be sought from the legal guardian or parent(s) and the child who would like to join the trial.

6.2. Randomisation

After patient eligibility has been confirmed and informed consent has been received, the patient can be randomised into the trial. Randomisation forms will be provided to investigators and should be used to collate the necessary information prior to randomisation. All questions and data items on the randomisation form must be answered before a patient can be randomised. If data items are missing, randomisation cannot continue until the information is available. Once all eligibility criteria and randomisation form data items have been provided, randomisation can occur and a Trial Number can be provided to the site.

Randomisation will be provided by a secure online randomisation system at Birmingham Clinical Trials Unit (BCTU) (available at https://ghd.bctu.bham.ac.uk/). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial on the GHD Reversal Trial Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the online system using another person's login details.

The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. Alternatively, patients can be randomised by telephoning the Trial Manager directly on +44 121 415 9131, Monday to Friday 09:00 to 17:00 UK time (excluding bank holidays and University of Birmingham closed days).

Patients will be randomised at the level of the individual in a 1:1 ratio to either GH+ (continue growth hormone therapy) or GH- (discontinue growth hormone therapy). A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- Tanner stage (B2 (females) or 6-<9 ml testicular volume of the largest testicle (males) vs B3 (females) or 9-12 ml testicular volume (males)
- Sex (male vs female)
- Participating centre

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment than they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the responsible clinician, randomising clinician (if different to responsible clinician), local PI, local Research Nurse, the Chief Investigator, National Coordinator for Austria, the Sponsor and the GHD Reversal Trial mailbox. A copy of the randomisation form will be sent to BCTU for data transcription accuracy checks.

6.3. Informing the participant's GP

If agreed on the ICF, the participant's GP (family doctor) and/or community paediatrician will be notified of the child's participation in the GHD trial, using the GHD Reversal Trial GP Letter.

6.4. Blinding

Due to the nature of the intervention (i.e. cessation of GH treatment administered via a daily injection) attempts at blinding would only be possible if the participants received a placebo daily injection. This would lead to an unrepresentative quality of life outcome as it would not reflect practice of removing daily injections. Further the discomfort, inconvenience and infection risk posed by these continued placebo injections are not considered ethical by the clinical leads. Due to the objective nature of the primary outcome (height) the lack of blinding should not affect the outcome of this trial, however to try and reduce the possibility of any bias we have specified instructions on measurement in section 10.5 of the protocol.

7. TRIAL TREATMENT / INTERVENTION

7.1. Treatment(s) and Dosing Schedule

7.1.1. Investigational Medicinal Product

The following licensed medications are the currently available growth hormone treatment preparations with the active ingredient Somatropin, as detailed in the British National Formulary for Children (BNFc). These will be discontinued in those participants randomised to the experimental arm (GH-):

Figure 1: GHD Reversal Trial – Somatropin licensed medications

Humatrope
Genotropin (MiniQuick, GoQuick)
Norditropin (Nordiflex, Simplexx, FlexPro)
NutropinAq
Omnitrope (Pen, SurePal)
Saizen
Zomacton

7.1.2. Control Arm (GH+)

Participants in the control arm (GH+) will resume receiving their GH treatment at a level prescribed by their clinical care team (following the minimum 4-week discontinuation period required prior to randomisation) and will be followed up at 6-monthly intervals until near FH or until the 36 month follow-up assessment*.

7.1.3. Experimental Arm

Participants in the experimental arm (GH-) will not resume GH treatment and participants will be followed up at 6-monthly intervals until near FH or until the 36 month follow-up assessment*.

* *The final recruit's 36 month assessment will be the end of the follow-up period. Participants who have not reached the near FH criteria can have 6 monthly visits (including past their own 36 month assessment) until the due date of the final participant's 36 month assessment.*

7.2. Drug Interaction or Contraindications

Somatropin is very well tolerated. There are no drug interactions or contraindications of note for somatropin other than those mentioned in the licensing label, however as stated in the exclusion criteria, patients must not have taken prednisolone or dexamethasone during the (minimum) 4-week GH discontinuation period prior to GH re-test. Additionally, all patients randomised into the trial will have been previously exposed to somatropin for several years, and will have completed the minimum 4-week discontinuation period. Co-medications (specified as pertinent to the trial by the Clinical leads) will be documented on the GHD Reversal Trial case report forms (eCRFs).

7.3. Accountability Procedures

Compliance with the randomised treatment allocation will be evaluated at each clinic assessment. Participants and/or parents/guardians in both treatment arms will be asked to report all GH therapy taken since the last clinic assessment irrespective of the arm the participant was randomised to. Details of any medication taken will be documented in the source data and on the trial eCRFs. This will identify any cross over between arms, any missed doses in the GH+ trial group, and any doses of GH taken by participants in the 'withdrawal' arm.

In the GH+ arm, participants will also be asked to indicate, via specified percentage ranges, how much of their prescribed GH they have taken. This measure of compliance will also be captured in the source data and reported on the eCRFs.

The GH- group should refrain from GH administration throughout the period of the trial unless clinically indicated. Non-compliance within this trial arm would be unlikely since patients who have stopped GH treatment cannot restart the treatment without a prescription, as GH is regarded in the same light as a controlled drug. Participants within the GH- group who do take GH therapy will remain in the trial to ensure accurate analyses can take place.

7.4. Treatment Modification

For the GH+ arm, growth hormone treatment is generally safe, and these patients will have been on the treatment for a number of years prior to cessation/recommencement of growth hormone. The dose used will be at the discretion of the treating clinician with growth rates and IGF-1 concentrations used to inform optimal dosage.

For the GH- arm, if there is clinical indication (e.g. IGF-1 below normal range & GH re-test with peak <6.7 µg/L) 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.

7.5. Cessation of Treatment/Continuation after the Trial

Participants will be deemed to have reached the end-point of this study when they attain 'Near FH'*. This is defined as growth velocity less than 2 cm per year (as calculated by the GHD Reversal Trial database growth velocity calculator) and a bone age (as determined by

BoneXpert analysis of hand X-rays) of a minimum 14 years in females and 16 years in males. This applies to both trial arms. At this point, the period of defined intervention will cease. For the purposes of the trial, participants will not be considered to be on trial treatment after reaching 'Near FH' (growth rate <2 cm/yr alongside attaining the required bone age).

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 follow-up period for the trial will end no later than the final participant's 36 month assessment. No further follow-up visits will be carried out after the final participant's 36 month assessment, including for participants who have not yet reached near FH.*

7.6. Treatment Supply and Storage

As this is a withdrawal study there will be no IMP to source or label in the experimental arm. Participants randomised to the GH+ arm will continue growth hormone as prescribed in routine clinical practice and at the discretion of their responsible clinician. Participating hospital or community pharmacies will be responsible for the continued supply of medication for participants in the GH+ arm throughout the trial, as per routine local clinical practice. The medication will be commercial stock in standard packaging. As the medication is a continuation of the participants' standard treatment from the local pharmacy's own stock, it will not be labelled as an IMP.

Regulation 46 of The Medicines for Human Use (Clinical Trial) Regulations 2004 allows for a particular situation where specific trial labelling is not required. This applies to trials of marketed products being (a) used within the terms of their marketing authorisation, (b) dispensed to a subject in accordance with a prescription given by an authorised health care professional and (c) labelled in accordance with the regulations that apply to dispensed relevant medicinal products. IMPs in the GHD Reversal Trial are marketed products being used within the terms of their marketing authorisation. They will be dispensed to the participant in accordance with a prescription given by an authorised health care professional (the participant's responsible clinician) and will be labelled in accordance with the regulations that apply to dispensed relevant medical products. The medication will be commercial stock in standard packaging. Therefore, specific trial labelling is not required.

The IMP to be used in the GHD trial can be labelled with a standard pharmacy dispensing label. This will be clearly documented in the submission in support of the Clinical Trials Authorisation (CTA) application.

Temperature monitoring should follow local pharmacy practice and deviations need not be reported to the GHD Trial Manager.

8. OUTCOME MEASURES AND TRIAL PROCEDURES

8.1. Primary Outcome

Near Final Height in Standard Deviation Score (FH SDS)

8.2. Secondary Outcomes

Growth Related:
The proportion of children reaching normal adult height (- 2SD)
The proportion reaching mid-parental Target Height (- 2SD)
Difference in child's Target Height minus near Final Height (in Standard Deviation Score and centimetres)

Bone Related:
Bone age delay at near Final Height
Bone age acceleration between enrolment and near Final Height
Bone health index at near Final Height

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

Adverse Events
Number of adverse events in each arm

Health Economics:
Cost per percentage of children in each arm achieving Target Height
Cost per Quality Adjusted Life Year gained

Qualitative Research:
Trial acceptability (parents, patients and recruiting site staff)
Reasons for declining participation in the trial
Parent and patient experience of the trial and treatment pathways

8.3. Study Procedures

In order to minimise patient burden, where possible the patient should be consented, randomised, and the baseline assessment completed all on the same day.

The baseline visit should include the following:

- Confirmation of inclusion and exclusion criteria
- Informed consent/assent
- Randomisation and allocation of trial number
- Prescription of growth hormone (if randomised to continue treatment), recording the preparation and dose prescribed
- Concomitant medication related to growth hormone deficiency
- Relevant medical history should be obtained. This includes:
    - Mid-parental TH, using the following formula; TH = (Mother's height + Father's height)/2 +/- 6.5 cm
    - Date of GHD diagnosis, serum IGF-1 at diagnosis and assay used, peak GH in first and second GH stimulation test at diagnosis (and diagnostic peak GH cut-off used at diagnosis), presence/absence of sex-steroid priming before each GH test
    - Date GH therapy started, GH preparation taken, last dose in µg/kg/day, and date of last dose taken before re-test
- Physical examination including height, weight and Tanner stage
- Review and recording of routine re-test results: GH stimulation test, presence/absence of sex-steroid priming before GH stimulation test, and serum IGF-1
- Biochemistry: fasting lipids (serum triglyceride and total serum cholesterol)
- Bone age and health assessment: hand X-ray (non-dominant hand)
- HRQoL: CHU-9D patient completed questionnaire

Each follow up visit has a +/- 14 day window and (months 6, 12, 18, 24, 30, 36 and subsequent 6 monthly visits, if required) should include the following:

- Physical examination including height, weight and Tanner stage. Height will be used to calculate annualised growth velocity at each time point to ensure near FH is identified
- Compliance check: crossover between trial arms will be monitored, with GH therapy received (preparation and dose) being recorded for all trial participants. In addition, for the GH+ arm, the percentage of treatments missed will be recorded as a patient reported measure.
- Concomitant endocrine medication related to growth hormone deficiency
- Adverse events will be recorded, as outlined in this protocol
- HRQoL: CHU-9D patient completed questionnaire

The following study procedures will be carried out in addition at specific time points:

- If a patient within the GH- trial arm (not receiving growth hormone therapy) 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 (serum triglycerides and total serum cholesterol) will be measured at the 36 month assessment (or near FH)
- Bone age and bone health index will be measured via a hand X-ray (non-dominant hand) at the 36 month assessment (or near FH).
- A GH stimulation test will be conducted at the 36 month assessment (or near FH)

8.4. Schedule of Assessments

Figure 2: GHD Reversal Trial Schedule of Assessments

Visit	*Screening*	*Baseline*	*Month 6 + or – 14 days*	*Month 12 + or – 14 days*	*Month 18 + or – 14 days*	*Month 24 + or – 14 days*	*Month 30 + or – 14 days*	*Month 36*** + or – 14 days*
*Pre-randomisation GH stimulation test**	X							
*Pre-randomisation serum IGF-I**	X							
Eligibility check	X	X						
Valid informed consent/assent		X						
Relevant medical history#		X						
Randomisation to GH+ or GH-		X						
Allocation of trial number		X						
Prescription of GH (if GH+)		X						
Height†		X	X	X	X	X	X	X
Weight		X	X	X	X	X	X	X
Tanner stage	X	X	X	X	X	X	X	X
Serum IGF-1			X	X		X		X
GH stimulation test (if GH-)~			X					
Fasting lipids		X						X
*Growth hormone compliance check***		X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X
Adverse event reporting			X	X	X	X	X	X
Hand X-ray		X						X
GH stimulation test (at near FH)								X
CHU-9D questionnaire		X	X	X	X	X	X	X
Collection of Health Economics Data			X	X		X		X

*** Patients will be followed up until 'Near FH (growth rate <2 cm/year & bone age of 14 and 16 for males and females respectively). Given the usual duration of pubertal growth until near FH is reached, three years follow-up has been allowed for, however if patients do not reach near FH by three years this may be longer.*

 # Relevant medical history to include:

- *Date of birth (DOB)*
- *Gender*
- *Date of GHD diagnosis*
- *Serum IGF-1 concentration (unit) at diagnosis*
- *IGF-1 assay used at diagnosis*
- *Peak GH in 1st GH stimulation test (µg/L) at diagnosis*
- *Peak GH in 2nd GH stimulation test (µg/L) at diagnosis (if applicable)*
- *GH stimulation test used at diagnosis*
- *Presence/absence of sex-steroid priming before each GH stimulation test*
- *Diagnostic peak GH cut off used at diagnosis*
- *Drug – which Growth hormone preparation, and last dose before re-testing (mg/kg/day)*
- *Date of GH therapy start*
- *Mid-parental TH = (Mother's height + Father's height)/2 +/- 6.5 cm*

**Conducted after minimum 4-week discontinuation period*

***Growth hormone compliance check to include recording of GH dose (mg/kg/d) at each time point including baseline, and to check for any cross over between trial arms, and missed doses in the GH+ arm, from 6 month assessment onwards.*

~GH re-test at 6 month assessment in GH- therapy group triggered by suboptimal growth and low serum IGF-1 only.

†Height to be measured as per procedure in section 10.5 of this Protocol.

8.5. Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants and/or parents/guardians should be asked about their ongoing willingness to continue participation at every visit. Willingness to continue participation should be documented in the child's medical notes.

Participants and/or parents/guardians must be aware that they can freely withdraw (discontinue participation) from the trial (or part of the trial) at any time, without giving a reason and that the medical care of the child will not be affected in any way. A participant who wishes to cease to participate in a particular aspect of the trial, will be considered as having changed their status within the trial.

The changes in status within the trial are categorised in the following ways:

- Withdraw from trial intervention:
  The participant and/or parent/guardian on behalf of the participant would like to withdraw from the intervention treatment (i.e. would like to recommence or halt GH administration), but is willing to be followed up in accordance with the schedule of assessments and for long-term outcomes (i.e. the participant and/or parent/guardian has agreed that data can be collected and used in the trial analysis).
- No trial related follow-up:
  The participant and/or parent/guardian on behalf of the participant does not wish to attend trial visits in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits and for long-term outcomes (i.e. the participant and/or parent/guardian on behalf of the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes). For GH- patients, this will include returning to standard of care.
- No further data collection:
  The participant and/or parent/guardian on behalf of the participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data that has been processed in interim analyses prior to the withdrawal can be retained, to ensure that any interim analyses that have been performed can be replicated if required).

The details of withdrawal or change of status within trial (date, reason and category of status change) should be provided, when possible, via trial exit/change of status form within the eCRF and clearly documented in the source documents.

9. ADVERSE EVENT REPORTING

9.1. Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with Regulation (EU) No. 536/2014 (Clinical Trial Safety Reporting requirements), the Medicines for Human Use Clinical Trials Regulations (2004) and its subsequent amendments, the UK Policy Framework for Health and Social Care (2017), and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed below in Figure 3.

It is routine practice to record AEs in the patient's medical notes. It is also recommended that this includes the documentation of the assessment of severity, seriousness and causality (relatedness) in relation to the intervention(s) in accordance with the protocol. The assessment of causality should be made with regard to the Reference Safety Information (RSI) as follows for the GH+ arm: Genotropin 5.3mg powder and solvent (Pfizer limited) Summary of Product Characteristics (SmPC) Revision of text date 06/2022, section 4.8 Undesirable Effects.

Figure 3: Adverse Event Definitions

Term	Abbreviation	Description
Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: • Results in death or is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • May have caused congenital anomaly/birth defect • Or is otherwise considered medically significant by the Investigator**

		*Life-threatening in this context refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more serious. **Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.
Serious Adverse Reaction	SAR	An Adverse Reaction which also meets the definition of a Serious Adverse Event
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.
Source data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a

		clinical trial necessary for the reconstruction and evaluation of the trial

9.2. Adverse Events (AE)

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

This list has been formulated taking into consideration the side effects documented for somatropin within the BNFc, the undesirable effects listed within the RSI (Genotropin 5.3mg powder and solvent (Pfizer limited) Summary of Product Characteristics (SmPC) Revision of text date 06/2022 and from clinician experience of halting GH therapy.

These AEs will be detected from patient-reported symptoms or clinical records during follow up. Collection of these AEs will help indicate whether the trial intervention is associated with increased adverse events.

9.3. Serious Adverse Advents (SAE)

9.3.1. Events that require expedited (immediate) reporting

SAEs will be recorded in all participants. Investigators will report all SAEs that are defined in the protocol (see *Figure 3: Adverse Event Definitions*) as an event which requires expedited reporting (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 within the participant medical notes.

9.3.2. Monitoring pregnancies for potential Serious Adverse Events

There is no identified risk of congenital anomalies or birth defects in the offspring of people receiving GH therapy. However, screening for pregnancy following each local hospital's usual practice will be carried out for female participants at each trial assessment. In the event that a female participant becomes pregnant during the course of trial follow up, a pregnancy notification form should be completed as part of the safety reporting procedures, and returned to the Trials Office.

To report a pregnancy, please complete the Pregnancy Notification Form online via the GHD Reversal trial database.

Details of the outcome of the pregnancy should be provided on a follow-up Pregnancy Notification Form, as long as consent has been given by the participant. A congenital anomaly or birth defect will need to be reported as an SAE.

9.4. Reporting period

The reporting timeframe for adverse events is from the date of randomisation until the participant reaches near FH or otherwise exits the study. The reporting timeframe for serious adverse events is from the date of randomisation until the GH stimulation test is conducted at near FH. This will provide a minimum 4-week wash out period for any participants that have been receiving GH therapy.

9.5. Reporting Procedure – At Site

9.5.1. Adverse Events

Adverse events should be recorded from randomisation until near FH, on the GHD Reversal Trial eCRF.

9.5.2. Serious Adverse Events

AEs which meet the definition of serious should be reported as an SAE on the GHD Reversal Trial SAE Form (a paper copy must be completed and sent to the GHD Reversal trial team at BCTU).

Relatedness and severity of the SAE will be assessed by the Principal Investigator (or medically qualified delegate). The following categories outlined in *Figure 4: GHD Reversal Trial SAE causality categorisation* will be used to define the relatedness (causality) of the SAE:

Figure 4: GHD Reversal Trial SAE causality categorisation

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely	
Possibly	There is some evidence to suggest a causal relationship, however, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship; there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant events or medication)	Unrelated
Not related	There is no evidence of any causal relationship	

On becoming aware that a participant has experienced an SAE, the Investigator or delegate(s) should report the SAE to their own Trust in accordance with local practice and to the BCTU trials office.

To report an SAE to the BCTU office, the Investigator or delegate(s) must complete, date and sign the GHD Reversal Trial SAE form.

To report an SAE email the SAE Form to: GHDReversal@trials.bham.ac.uk.

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. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a

unique SAE identification number within 1 working day, the site should contact the BCTU trials team. The site and the BCTU trials team should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

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.

9.5.3. Provision of follow-up information

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. A copy of all SAE forms submitted for an event will be held at the BCTU trials office, and the original documents should be held in the Site File.

9.6. Reporting Procedure – BCTU Trials Office

On receipt of an SAE form from the site, the BCTU trials team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the completed unique reference number) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the actual SAE in the TMF.

On receipt of an SAE Form the Trials Office will forward it, with the unique reference number, to the CI or delegate who will independently determine the causality of the SAE. For the purposes of this trial, the CI (Prof Dattani) will assess all SAEs, unless unavailable or an SAE occurs at the CI's site. In these instances, the Austrian National Coordinator (Prof Högler) will take responsibility for reviewing the SAE. If Prof Högler and Prof Dattani are both unavailable, a qualified delegate will assess the SAE. An SAE judged by the PI (or delegate) or CI or delegate(s) to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The causality assessment given by the PI (or delegate) will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI's (or delegate's) causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI or delegate(s) will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the approved version of the RSI: Genotropin 5.3mg powder and solvent (Pfizer limited) Summary of Product Characteristics (SmPC) Revision of text date 06/2022, section 4.8 Undesirable Effects, it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

9.7. Reporting to the Competent Authority and main Research Ethics Committee

9.7.1. Suspected Unexpected Serious Adverse Reactions

BCTU will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA), the REC, and the Sponsor (UCL), within 7 days of being made aware of this SUSAR.

These reports will be shared with the Austrian coordinating centre who will report to the Austrian competent authority, Bundesamt für Sicherheit im Gesundheitswesen (BASG), and other required regulatory bodies. Detailed follow-up information will be provided to the MHRA, the REC, the Sponsor, and the Austrian coordinating centre (for reporting to BASG and other required regulatory bodies), within an additional 8 days.

All other events categorised as non-life threatening SUSARs will be reported within 15 days.

9.7.2. Serious Adverse Reactions

BCTU will report details of all SAEs (including SUSARs) to the MHRA, the REC and the Sponsor (UCL) annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR).

The DSUR will be shared with the Austrian coordinating centre who will report to BASG and other required regulatory bodies.

9.7.3. Adverse Events

Details of all AEs will be reported to the MHRA (and BASG via the Austrian coordinating centre) on request.

9.7.4. Other safety issues identified during the course of the trial

The MHRA, BASG, main REC and the Sponsor (UCL) will be notified immediately if a significant safety issue is identified during the course of the trial.

9.8. Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to PIs. A copy of any such correspondence should be filed in the Site File.

9.9. Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review data from all SAEs as part of the DMC report.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Figure 5: GHD Reversal Trial Source Data

Data	Source
Participant Reported Outcomes (CHU-9D)	The original participant-completed paper CHU-9D questionnaire is the source. These will be kept with the participant's trial record at site.
Lab results/X-rays	The original lab reports and/or X-ray images (which may be electronic) are the source and will be kept and maintained, in line with normal local practice. Information will be uploaded onto eCRFs on the trial database hosted at the University of Birmingham.
Clinical event data	The original clinical notes are the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. Information will be uploaded onto eCRFs on the trial database hosted at the University of Birmingham.
Qualitative Research data	Obtained by interview directly with the participants via audio recordings – these recordings will be transcribed clean verbatim for analysis. Both the recordings and transcriptions will be source data and uploaded to the study database hosted at the University of Birmingham.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers hosted at the University of Birmingham as part of the randomisation and data entry system.
Screening data	The original record of patient screening, contained within the medical notes, is the source. Information will be uploaded onto the trial database hosted at the University of Birmingham.
Drop out	Where a participant expresses a wish to withdraw, the conversation should be recorded in the medical records, and the relevant trial withdrawal documentation completed and uploaded onto eCRFs

	on the trial database hosted at the University of Birmingham.

10.2. Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual subject. For the GHD Reversal trial, the CRF will be the record on the online database (i.e. the eCRF). Worksheets mirroring the eCRF (as displayed on the online database) will be provided to sites to aid with data collection, but these will not form part of the CRF. The exceptions to this are the completed paper randomisation forms and paper SAE forms (the data from these forms will be recorded on the trial database to mirror the paper CRFs, but the paper record will form part of the CRF). The data held on the completed CRFs (and/or eCRFs) are the sole property of the respective PIs whilst the data set as a whole is the property of the Sponsor and should not be made available in any form to third parties, except for authorised representatives or appropriate regulatory authorities, without written permission from the Sponsor. Appropriate data sharing requests will be considered by the Sponsor (UCL) and the BCTU Data Sharing Committee.

It will be the responsibility of the PI to ensure the accuracy of all data entered in the eCRFs and confirm accordingly. The GHD Reversal Trial Signature and Delegation Log will identify those personnel with responsibilities for data collection.

The CRFs will comprise the following Forms:

Figure 6: GHD Reversal Trial Data Collection Forms

Form Name	**Schedule for Submission**
Screening form	Prior to randomisation
Randomisation form	At the point of randomisation
Baseline form	Post randomisation
CHU-9D	Following trial appointment with patient at appropriate time point
Follow up form (6, 12, 18, 24, 30, 36 and subsequent 6 monthly forms, if required)	Following trial appointment with patient at appropriate time point.
Near final height form (at 36 months or when near FH is reached)	Following trial appointment with patient at appropriate time point.
Medication Form	Available throughout follow-up, submission at end of follow-up/near FH.

Healthcare Contacts Form (6, 12, 24 and 36 and subsequent 12 monthly forms, if required)	Following trial appointment with patient at appropriate time point.
Serious Adverse Event Form	Emailed within 24hrs of research staff at site becoming aware of event.
Pregnancy Notification Form	Within 14 days of site becoming aware of the pregnancy.
Trial exit/Change of status CRF	At the point of withdrawal or death

Data reported on each form will be consistent with the source data and any discrepancies must be explained. All missing and ambiguous data will be queried via a data clarification form (DCF) system. Trust staff delegated to complete CRFs will be trained to adhere to the latest version of the GHD Data Management Guidelines for Sites.

For the GHD Reversal Trial, CRFs will be an electronic record completed at site by those at site delegated the task of doing so. The exception to this are the completed paper randomisation forms and paper SAE forms, only. Forms will be considered "complete" once all data fields have been either completed unambiguously or it has been made explicit that the data are unobtainable.

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the site PI logging in to the GHD Reversal trial database and providing their signature on the eCRF.

Data should be submitted in a timely manner. Sites will receive automated email reminders for upcoming follow-up assessments (these dates are generated by the expected schedule for patients' follow-up appointments, based upon their randomisation date). If data have not been provided within 2 weeks of the scheduled date for a patient's follow-up assessment then automated reminder emails will be sent to sites fortnightly informing them that the data is overdue. If the data have still not been received within 6 weeks then trial staff from BCTU will directly contact the site to ascertain the reason for the delay. At 10 weeks from expected submission if the data still have not been received this may be escalated to site's senior management and further monitoring, potentially including BCTU representatives visiting sites, may be triggered.

10.3. Participant Completed Questionnaires

Data collected from CHU-9D will be used to inform the cost per QALY gained outcome measure. At baseline and each 6 monthly assessment the CHU-9D will be completed directly by the participant. Participants should be encouraged to respond to all questions but can refuse to answer any, or all, of the questions should they wish. Where a questionnaire is returned to the local research staff, in person, with some questions unanswered, research staff should clarify with the participant that they have chosen not to respond specifically to the unanswered questions and that they have not simply missed them in error.

Once the questionnaire has been completed by the participant and checked by site staff, the matching CHU-9D eCRF should be completed on the GHD Reversal trial database by staff at site who have been delegated the responsibility of doing so.

10.4. Hand X-Ray Process

X-Rays of the patient's non-dominant hand (dominant hand is acceptable if non-dominant is not available) should be taken at baseline and at near FH to inform the primary outcome and several secondary outcomes. The same hand must be used for each hand X-ray that is performed on a patient during the trial.

The X-ray images will be sent for central analysis. In the UK, the scans will be sent securely from the NHS hospital trust to Great Ormond Street Hospital (GOSH) for analysis, in Austria the scans will be sent securely to Kepler Universitätsklinikum for analysis. This analysis will be undertaken using BoneXpert software. Once the analysis has been performed, the X-ray image will be securely returned to the patient's trial site with an overlay of the data required for the trial. Once this image is received back at the patient's trial site, the clinical team at site should enter the relevant data onto the relevant GHD Reversal Trial eCRF.

X-Rays received at GOSH and Kepler Universitätsklinikum will be deleted no longer than 60 days after receipt.

10.5. Height Measurement Procedure

In order to try and minimise any potential bias during the measurement of patient height, the following procedure must be followed. There must be two clinic staff members experienced in the measurement of children conducting each measurement. The measurements must be repeated, with repositioning of the child between each measurement, until three consecutive measurements are within a 0.5 cm range. Each measurement must be recorded in the patient's medical notes, and the final result to be recorded on the patient's trial CRF must be the mean taken from the three consecutive measurements that are within a 0.5 cm range.

10.6. Data Management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and validation will be agreed between the trial manager, statistician and programmer and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data will be queried using a data clarification system in line with the GHD Reversal Trial Data Management Plan, and will primarily focus on data required for informing trial outcome analysis and safety reporting. Single data entry with central monitoring will be employed. Staff at site (as delegated on the GHD Reversal Trial Signature and Delegation Log) will enter and submit data on an eCRF online (except for serious adverse events). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of CRF completion as detailed on the GHD Reversal Trial Signature and Delegation Log. These unique log-in

details must not be shared with other staff and in no circumstances should staff at sites access the trial database using another person's login details. The system will include data validations to improve data quality (e.g. to prevent nonsensical dates or numerical values). Changes to the data on the system will be documented and attributable (with a reason for the change documented) and will be made by local site staff, with the exception of SAE form changes, which will be made by BCTU staff. SAE Forms will be emailed directly to the trial office for trial office staff to enter the data onto the eCRF.

Due to data entry occurring predominantly at site, few self-evident corrections of the data will be undertaken at BCTU. The following self-evident corrections will be allowed for data entered on behalf of sites at BCTU:

- Dates: amendment of incorrect year (where the error is obvious) for forms completed at the start of a new year to allow online data entry.
- Dates: Amendment of date format to allow online data entry (e.g. DDMMYYYY instead of DDMMMYYYY as specified on CRF)
- Spelling: Correction of general spelling mistakes with reference to an English dictionary.
- Trial number: Where the trial number is incorrectly recorded on the paper CRF, but the patient can be unequivocally identified from the other patient identifiers on the form, the number may be amended to allow online data entry.

Self-Evident corrections will only be made to non-critical data items, and will be agreed with the PI prior to implementation.

10.7. Data Security

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham are registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the trial. The Trial Centre has arrangements in place for the secure storage and processing of the trial data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate storage of non-identifiable data etc.
- Network security measures: including site firewalls, antivirus software, separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role-based security controls.
- Operational Processes: the data will be processed and stored within the University of Birmingham.

- Data processing: Statisticians will only have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - Periodic IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.8. 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.

Prior to long term archiving, the TMF will be stored at the Trial Office under controlled conditions. Long-term offsite data archiving facilities will be considered for storage after this time; data will be stored for at least 25 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

The requirements of the CI will be covered in the signed Collaboration Agreement between UCL, UoB and JKU. This Collaboration Agreement contains a subcontract detailing the delegation of duties between UCL, UoB and JKU, and specifies which duties the CI is responsible for. In addition, all local PIs will be asked to provide to BCTU the necessary agreements, including but not limited to, a GHD Reversal Trial Signature and Delegation Log, a current CV (signed and dated in adherence to local Trust policy) and a GCP certificate (adhering to local Trust policy on GCP renewal). All members of the site research team are required to sign the GHD Reversal Trial Signature and Delegation Log, which details which tasks have been delegated to each member of staff by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a physical or virtual (tele/video-conference) meeting, at which key members of the site research team are required to attend. This meeting will cover aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with a GHD Reversal Trial Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

11.2. Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU and as documented in the monitoring plan.

11.3. Onsite Monitoring

For this trial we will monitor all sites in accordance with the GHD Reversal Trial Risk Assessment and Monitoring Plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered by (but not limited to) poor CRF return, poor data quality, excessive number of participant withdrawals or deviations. If a monitoring visit is required, the Trials team will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the GHD Reversal Trial staff access to source documents as requested. If required, monitoring visits will be conducted by appropriate members of the trial management team in each member state.

11.4. Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming ICFs and eCRFs (ICF, GHD Reversal Trial Randomisation Form, and GHD Reversal Trial SAE Form will be completed on paper, all other CRFs will be eCRFs, completed on the trial database) for compliance with the protocol, data consistency and missing data at a frequency and intensity determined by the Data Management Plan. Sites are required to send in copies of

signed ICFs for central review for all participants and their parents/guardians who provide explicit consent. This will be detailed in the monitoring plan.

Sites will be sent DCFs requesting missing data or to clarify inconsistencies or discrepancies.

11.5. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.6. Notification of Serious Breaches

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified may be reported to the TMG and TSC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC, MHRA and BASG.

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a "serious breach" is a breach which is likely to effect;

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial

Sites are therefore requested to notify the Trials office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the Competent Authority where required and in undertaking any corrective and/or preventive action.

12. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture, including resolution of data queries via DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The BCTU trial team will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. The Austrian co-ordinator will notify the relevant Austrian bodies.

Where the trial has terminated early, the Trials Office will inform the MHRA and REC within 15 days of the end of trial. The Trials Office will provide them with the Clinical Trial Summary Report within 12 months of the end of trial. The Austrian co-ordinator will notify the relevant Austrian bodies.

A copy of the end of trial notification as well as the summary report will also be sent to the Sponsor (UCL). At the appropriate time, these will be sent to the MHRA, and REC, as well as the Austrian co-ordinator who will notify the relevant Austrian authorities.

13. STATISTICAL CONSIDERATIONS & SUB-STUDY ANALYSES

13.1. Sample Size

Determination of non-inferiority margin was carefully considered, following extensive consultation. A questionnaire was sent to all investigators, British Society for Paediatric Endocrinology and Diabetes clinical study group members and a patient support group representative (n=34), giving several options for 'acceptable deficit' in various FH outcomes. The outcome options were 1) the percentage of children reaching normal adult height (0+/-2SD), 2) the percentage reaching mid-parental TH (0 +/- 2SD), and 3) actual difference in FH (SDS/cm).

FH Standard Deviation Score (near FH-SDS) was selected as the primary outcome, with a non-inferiority margin of 0.55 SD. As a guide, in a population-based register[27], mean near FH SDS was approximately -1.5 (+/- 1SD) in GH-treated children.

Whilst the percentage of children reaching mid-parental TH[1] was the most popular outcome amongst respondents, data were not available to inform a sample size calculation. However, all the above options to express FH will be analysed in this trial as secondary outcomes. Other secondary outcomes are HRQoL, lipid profile, cost-effectiveness and the bone health index (assessing effect of GH+/GH- on bone accrual using BoneXpert software).

For the primary outcome measure of near FH-SDS with a non-inferiority design comparing means and assuming equal variance, a non-inferiority margin of 0.55 near FH-SDS, a one-sided test with alpha=0.025 and 90% power, a group size of 57 (total n=114) would be needed (calculated using the SSI procedure in Stata 13). This calculation was based on a near FH-SDS (SD) of -1.6 (0.9) using data from a population based registry for patients with idiopathic growth hormone deficiency treated with growth hormone and completing the scheduled treatment[27]. The non-inferiority margin is based on clinical opinion. Additional observational studies gave consistent results. Using LMS growth software, a 0.55 height SDS score (using British 1990 Growth Charts[45]) approximates to 3.8 cm for boys and 3.3 cm for girls at age 23. With 17% allowance for withdrawal and loss to follow up, a total sample size of 138 is required.

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan (SAP) will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those treated with GH (25-35 µg/kg/day) versus those not treated with GH. Non-inferiority outcomes will be analysed using both intention to treat ((ITT) i.e. all participants will be analysed in the treatment group to which they were randomised, irrespective of compliance or other protocol deviation) and per protocol analyses (i.e. those participants who are considered adherent to their allocated intervention, as defined in the SAP). This is because an intention to treat analysis alone may bias results in favour of non-inferiority. Superiority outcomes will be analysed using ITT analyses only. For all primary and secondary outcome measures, summary statistics and differences between groups will be presented with 95% confidence intervals. Outcomes will be adjusted for the minimisation variables listed in section 6.2 and baseline values where appropriate. No adjustment for multiple comparisons will be made.

13.2.1. Primary Outcome Measure

The primary outcome measure is near FH-SDS (using the WHO Growth Charts[3]) and is considered a non-inferiority outcome. The groups will be compared using a linear regression model adjusting for the minimisation variables and baseline height SDS, to compare the mean FH-SDS between the GH+ and GH- group. The adjusted mean difference in FH-SDS will be presented alongside a 95% confidence interval. Non-inferiority for the primary outcome will only be concluded if the lower bound of the 95% confidence interval limit is above -0.55 for both the ITT and per-protocol analyses.

13.2.2. Secondary Outcome Measures

Growth and bone-related secondary outcomes will be considered non-inferiority outcomes and so will be analysed as per the primary outcome using both ITT and per-protocol analyses. Biochemistry and adverse event outcomes will be considered superiority outcomes and so will be analysed using ITT analyses only. Continuous outcomes will be analysed using linear regression models, adjusting for minimisation variables and baseline response (where applicable). Adjusted mean differences will be presented alongside 95% confidence intervals. Binary outcomes will be analysed using log binomial regression models, adjusting for minimisation variables, with both a log and identity link to obtain risk ratios and risk differences, respectively. P-values will only be reported for superiority outcomes. The number of participants who experience an SAE will be reported alongside the number of SAEs reported.

13.2.3. Subgroup Analyses

Subgroup analyses will be limited to minimisation variables: sex and Tanner stage, for the primary outcome only. Tests for statistical heterogeneity (e.g. by including the treatment group by subgroup interaction parameter in the regression model) will be performed prior to any examination of effect estimate within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

13.2.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the effect of any missing data. In brief this will include: a multiple imputation approach, using important variables to predict the FH SDS and a last observation carried forward (LOCF) approach, which assumes no change from the previous assessment.

A further sensitivity analysis will be conducted to assess the impact of participants who have not reached near FH by the end of the study. For the primary analysis, all participants will be included and for any participants who have not reached near FH, their height recorded at the end of study follow-up visit will be used. Although we anticipate this to be a rare event, we will conduct a sensitivity analysis (for the primary outcome only) which excludes any participants who have not reached near FH by the end of the study. Full details will be included in the SAP.

13.3. Internal Pilot and Stopping Rules

Based on national audit and survey data within centres, we estimate an average of 8-10 re-tests per year/centre and a reversal rate of 50%, based on the literature average of 49% (though with a wide range)[6-8, 17, 18], which is corroborated by a survey at Birmingham

Children's Hospital (n=55; 54% reversal, GH cut-off 5 µg/L). The "in principal acceptability" of the trial has also been addressed with a group of parents and patients. Of 24 parents and 20 patients with I-GHD responding to a feasibility questionnaire administered across several trial centres, 71% of parents and 60% of children stated that they would be willing to take part in the trial. Thus, we expect to recruit an average of 2.5 patients/year with early GHD reversal in each of the centres over 3.5 years.

To ensure the success of the trial, screening data will be kept on the GHD Reversal Trial database on the number of early re-tests, GHD reversers and recruits. No patient identifiable information will be collected at this stage. These data will be analysed and presented as part the Progress Report for the TSC. According to published standards, Amber and Red 'Stop/Go' criteria have been agreed with the Funder. Time points are calculated from first centre opening. Three Stop-Go criteria measurable in the first 12 months of the trial were identified as critical steps for the trial's successful recruitment (see *Figure 7: GHD Reversal Trial Stop/Go Criteria*). These were:

1. Recruitment of trial sites: We believe that there is a low risk that this will not be achieved, given that we have prior commitments to participate from the sites. Nevertheless, adequate site recruitment is critical to trial success. An Amber status at 6 months will trigger consideration of factors impeding site recruitment and a remedial action plan. A Red status at 12 months will stop the trial.

2. GHD reversal rate: This criterion will determine the size of the pool of eligible patients. An Amber warning will trigger an evaluation of any atypical factors in re-tested patients and an assessment of the feasibility of expanding site recruitment. A Red status at 12 months will stop the trial.

3. Recruitment rate of eligible (GHD reversed) patients: An Amber warning at 6 months will trigger consideration of barriers and facilitators of recruitment. This may include assessment of early signals from the qualitative trial. A recruitment action plan will be developed and implemented. A Red status at 12 months will stop the trial.

Figure 7: GHD Reversal Trial Stop/Go Criteria

Criterion	**Threshold**	**Risk Status**
Sites open		
At 6 months	<6 sites	AMBER
At 12 months	<12 sites	RED
GHD reversal rate (i.e. size of pool of eligible patients)		
After 20 patients tested	<20% (n=4)	AMBER
After 40 patients tested	<25% (n=10)	RED
Number of eligible (GHD reversed) patients recruited		
At 6 months	<15	AMBER
At 12 months	<30	RED

13.4. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the trial. The committee will meet prior to trial commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the trial based on this information will be ratified by the DMC. Details of the agreed plan will be written into the SAP. Further details of DMC arrangements are given elsewhere in the protocol.

13.5. Planned Final Analyses

The primary analysis for the trial will occur once all participants have either fulfilled the near FH definition (growth rate of <2 cm/year and have reached a bone age of 14 years (females) or 16 years (males)), or have completed the 36 month assessment, or have withdrawn from the study or been lost to follow-up and corresponding outcome data have been entered onto the trial database and validated as being ready for analysis.

All other outcome measure analyses will be undertaken when the final participant (as defined above) reaches their 36 month assessment.

13.6. Health Economics Analysis

The health economics analysis has two specific aims. The first is to assess the cost-effectiveness of GH discontinuation in the early re-testing scenario by estimating the cost per percentage of children achieving TH of GH- compared to GH+ over a 12-month period , and the second is to assess the cost-effectiveness of the new care pathway (early re-testing) compared to traditional care (late re-testing).

To assess the cost-effectiveness of no GH therapy (GH-) compared to GH therapy (GH+) in patients with GHD reversal; a cost-consequence analysis will initially be reported, describing all the important results relating to resource use, costs and consequences. Subsequently a trial-based cost-effectiveness analysis will be undertaken from an NHS/Personal Social Services (PSS) perspective to determine the cost per percentage achieving TH of GH- compared to GH+ over a 12-month period.

Resource use information will be obtained on all healthcare utilisation (primary care and secondary care) and will be obtained mainly from participant questionnaires. Unit costs will be obtained from standard sources and healthcare providers including the British National Formulary (BNF), PSSRU publication on Unit Costs of Health and Social Care and NHS Reference costs.

Mean costs and outcomes will be estimated for both the no GH therapy (GH-) and GH therapy (GH+) arms. Cost data are likely to be skewed, therefore, non-parametric comparison of means (e.g. bootstrapping) will be undertaken. Multiple imputation techniques will be used to deal with missing costs, in order to ensure that all eligible trial participants are included in the analysis.

Incremental cost-effectiveness ratios (ICERs) will be calculated and cost-effectiveness acceptability curves will be presented to estimate the probability that GH- is cost-effective for different willingness to pay thresholds.

The second objective of the health economics analysis is to determine the cost-effectiveness of the new care pathway (early re-testing) compared to traditional care (late re-testing)

using a decision analytic modelling approach. The model will determine the cost per percentage achieving TH and cost per additional quality adjusted life year (QALY) gained for the intervention (early re-testing) and usual care arm (late re-testing).

Data from the main trial and other published sources will be used to populate the model. An incremental cost-effectiveness analysis will determine the cost per percentage achieving TH and an incremental cost-utility analysis will be undertaken to estimate the cost per QALY gained. Both analyses will be conducted from an NHS perspective. Deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters. Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by conducting a probabilistic sensitivity analysis to estimate cost-effectiveness acceptability curves.

14. TRIAL ORGANISATIONAL STRUCTURE

14.1. Sponsor

University College London (UCL) is the Sponsor for the GHD Reversal Trial.

14.2. Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU) based at the University of Birmingham (UoB). Delegation of tasks to the BCTU, from the Sponsor, are documented as part of the Research Collaboration Agreement between the Sponsor (UCL) UoB, and Johannes Kepler University (JKU), in Schedule C – Delegation of duties. JKU is the national coordinating centre for Austria.

14.3. Trial Management Group

The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

14.4. Trial Steering Committee

A TSC will be created for the GHD Reversal Trial and will meet at least annually and as required depending on the needs of the trial. The TSC will include members who are independent of the investigators, their employing organisations, funders and sponsors.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will: provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the participants and provides appropriate feasibility data to the Sponsor and investigators. The TSC will consider and act, as appropriate, upon the recommendations of the DMC or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

14.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet at least annually as agreed by the Committee and documented in the Charter, unless there is a specific reason (e.g. safety phase) to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC, who will convey the findings of the DMC

to the Funder, Sponsor and MHRA as relevant. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. Please see section 13 of this protocol for details on interim analyses, internal pilot and stopping rules.

14.6. Finance

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) is funding this trial. Clinical Research Network (CRN) support will be sought.

15. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: *http://www.wma.net/en/30publications/10policies/b3/index.html*).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments, the Data Protection Act 2018 and subsequent amendments, the Human Tissue Act 2008 and the EU Clinical Trials directive) and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main REC prior to circulation and the start of the trial.

All correspondence with the MHRA, BASG and/or REC will be retained in the TMF/ISF. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. Equivalent progress reports will be produced by the International co-ordinating centre as required for the relevant Austrian regulatory bodies in accordance with the rules in that member state.

Before any participants are enrolled into the trial, the PI at each site is required to obtain local confirmation of capacity and capability from their Trust's R&D office (and Austrian equivalent). Sites will not be permitted to enrol participants until written confirmation of capacity and capability is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 and Regulation (EU) 2016/679 (General Data Protection Regulation).

Participants will always be identified using their unique trial identification number and partial DOB (month/year format) on the CRFs and in any correspondence. Parents/guardians and participants will give their explicit consent for the transfer of their consent form and will give explicit permission for BCTU to be sent a copy. This will be used to perform central monitoring of the consent process.

The local investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Interviews will be recorded with the consent of participants and transcribed clean verbatim for analysis. Transcripts will be produced by a UoB approved professional transcription company. A confidentiality agreement is in place between the transcription service provider and UoB to ensure data are handled securely. Audio files of interviews, consultations and transcripts will be uploaded to an encrypted, secure cloud server. Only members of the qualitative research team and the assigned transcriber will have access to the transcripts stored on the cloud. Once the files have been received by a member of the qualitative research team or the transcriber, they will be deleted from the cloud server. Analysis will be conducted with reference to recordings, transcripts and field notes taken at the time of the interviews. Any paper consent and contact details forms will be filed securely in a locked filing cabinet, in a locked room, at UoB by a member of the qualitative research team. The audio records of verbal consent and assent will be saved on an encrypted UoB server.

BCTU will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party. Representatives of the GHD Reversal Trial team and Sponsor may be required to have access to participants' notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

17. FINANCIAL AND OTHER COMPETING INTERESTS

There are no commercial repercussions related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

18. INSURANCE AND INDEMNITY

Indemnity arrangements for the GHD Reversal Trial will be undertaken by the Sponsor University College London (UCL).

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if

they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Note: The maximum number of participants recruited in Austria must not exceed 45 under the indemnity cover arranged for the Austrian sites.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients in the UK remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority. In Austria the responsibility for the care of the patients remains with the organisations (hospital sites) and is therefore indemnified through the organisations' usual patient insurance.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

19. POST-TRIAL CARE

Following completion of the trial patients will be managed according to the standard clinical care that is deemed appropriate by their responsible clinician.

20. ACCESS TO THE FINAL TRIAL DATASET

During the period of the study only the Data Monitoring Committee (DMC) will have access to the full trial dataset in order to ensure participant safety. Following publication of the findings, an aggregated, anonymised final trial dataset will be made available to external researchers upon approval from the Sponsor, the TMG and the BCTU Data Sharing Committee in line with standard data sharing practices for clinical trial data sets.

21. PUBLICATION POLICY

The GHD Reversal Trial protocol will be made publicly available via both the GHD Reversal Trial webpage hosted by the Trial Office and subsequently published in an appropriate journal, in advance of the final data set.

Upon completion of the trial and analysis of the final dataset, a Final Report to the Funder will be prepared.

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the co-investigators and authorship will be determined by the BCTU trial publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG prior to submission. Manuscripts must be submitted to the TMG in a timely fashion to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of BCTU/UoB, UCL, and JKU. Results of the trial will be disseminated by the trials unit to participating clinical centres, who will be asked to distribute this to the participants and the wider clinical community.

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