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Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation

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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Δ	change in (variable)
±	signifies the variability around a measure of central tendency (usually a mean). The associated value will be one standard deviation, unless stated otherwise
AACE	American Association of Clinical Endocrinologists
ANCOVA	analysis of co-variance
ANOVA	analysis of variance
Auxological	measurements pertaining to growth
BA	bone age. A measure of skeletal maturity, evaluated on the basis of the relative positions of the bones, generally in the left hand and wrist
BMD	bone mineral density
BMI	body mass index (kg/m^2)
BNF	*British National Formulary*
BSPED	British Society for Paediatric Endocrinology and Diabetes
CA	chronological age
CGD	constitutional growth delay
CGHAC	Canadian Growth Hormone Advisory Committee
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CRF	chronic renal failure
DARE	Database of Abstracts of Reviews of Effectiveness
DEC	Development and Evaluation Committee
DEXA	dual-energy X-ray absorptiometry
EQ-5D	EuroQoL-5 dimensions. A quality-of-life assessment instrument
FH	final height
FSH	follicle-stimulating hormone
FSS	familial short stature; genetic short stature. One of several synonyms for idiopathic short stature (ISS), along with normal short stature and constitutional growth delay (CGD), which are often used interchangeably
GFR	glomerular filtration rate
GH	growth hormone
GHD	growth hormone deficiency
GP	general practitioner
GV	growth velocity (generally cm/year)
GVSDS	growth velocity standard deviation score. Growth velocity relative to the distribution of growth in children of the same chronological age (or bone age, if specified)
HbA_{1C}	glycosylated haemoglobin

continued

continued

HtSDS	height standard deviation score. Height relative to the distribution of height in children of the same chronological age (or bone age, if specified)
HUI	Health Utility Index
ICER	incremental cost-effectiveness ratio
IC-GH	integrated concentration of GH
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor binding protein
IIH	idiopathic intracranial hypertension
ISS	idiopathic short stature
ITT	intention to treat
IU	international unit (3 IU = 1 mg)
KIGS	Pharmacia International Growth Database
LH	luteinising hormone
LHRHa	luteinising hormone-releasing hormone analogue
m^2	square metres (in this context referring to body surface area)
MAMC	mid-arm muscle circumference
met-hGH	methionyl human growth hormone
MRC	Medical Research Council
MRI	magnetic resonance imaging
NAH	near adult height
NCGD	non-constitutional growth delay
NCGS	National Cooperative Growth Study
NF	near final
NFH	near final height. Height measured when growth is assumed to be near completion (see appendix 7)
NFSS	non-familial short stature
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
NS	not statistically significant
OX	oxandrolone
PAH	predicted adult height. Extrapolating adult height from childhood height (see appendix 7 for further details)
PWS	Prader–Willi syndrome
QALY	quality-adjusted life-year
QoL	quality of life
QUOROM	Quality of Reporting of Meta-analyses
QWB	Quality of Well-being (Scale)
RCT	randomised controlled trial
rhGH	recombinant human growth hormone
s.c.	subcutaneous
SD	standard deviation
SDS	standard deviation score
SE	standard error
TS	Turner syndrome
TSF	triceps skinfold
TSH	thyroid-stimulating hormone
TSSS	Turner Syndrome Support Society
TW	Tanner–Whitehouse (standard based on normal population)
VAT	value-added tax

Executive summary

Background

Recombinant growth hormone (GH) is licensed for use in children with GH deficiency (GHD), Turner syndrome (TS), chronic renal failure (CRF) and Prader–Willi syndrome (PWS). GH is also used in conditions for which it is not licensed, such as idiopathic short stature (ISS).

In all five of these indications for GH treatment, affected children, if left untreated, can be about 12–36 cm (5–14 inches) shorter than the normal mean height as adults. The primary rationale for prescribing GH to children is to improve their short-term growth and/or their final height.

Epidemiology

Prevalence estimates suggest that, in England and Wales, there are approximately 28,500 children between the ages of 0 and 16 years who are affected with the conditions of interest (approximately 2900 children with GHD, 1970 with TS, 640 with CRF, 540 with PWS, and 22,450 with ISS). Only about 7% are currently being treated (approximately 2000 children), the majority (78%) having GHD, CRF or TS.

Objectives

This review considers the clinical effectiveness and cost-effectiveness of GH therapy in children with GHD, TS, CRF, PWS or ISS.

Methods

A systematic review of the literature and an economic evaluation were undertaken.

Data sources

The main electronic databases were searched, with English language limits, for the periods up to April 2001. Bibliographies of related papers were assessed for relevant studies, and experts were contacted for advice and peer review, as well as to identify additional published and unpublished references. Manufacturer submissions to the National Institute for Clinical Excellence were reviewed.

Study selection

Studies were included if they fulfilled the following criteria, which were applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

- Intervention was biosynthetic human GH (somatropin).
- Participants were children with one of five conditions: GHD, TS, CRF, PWS or ISS.
- Outcomes were final height and short-term growth responses to treatment, such as height standard deviation score and height velocity. Quality-of-life measures were reported if available.
- Designs were randomised controlled trials (RCTs) or systematic reviews of RCTs that assessed the effects of GH (compared with placebo or no intervention) based on any of the above patient-relevant outcomes. If final height was not an outcome in at least one of the RCTs for that condition, the best studies from lower down the hierarchy of evidence that reported final height were included. Economic evaluations of GH in children suffering from one of the five conditions were included in the review of cost-effectiveness if they included a comparator (or placebo) as well as both the costs and consequences (outcomes).

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of RCTs was assessed using Jadad criteria, and non-RCTs were assessed using modified Spitzer criteria. The internal validity of economic evaluations was assessed using the *BMJ* checklist, and external validity was assessed using a series of relevant questions.

Data synthesis

The clinical effectiveness of GH in children was synthesised through a narrative review with full tabulation of results of all included studies. In the economic evaluation, a cost-effectiveness model was constructed using the best available evidence to determine cost-effectiveness in a UK setting.

Results

Number and quality of studies

RCTs comparing GH with placebo or no treatment were included, and because final height data were rarely available in the context of RCTs, lower levels of evidence were included for final height only, using the highest level of evidence available within each condition. A total of 34 publications reporting 32 studies were included in the assessment of clinical effectiveness. Short-term growth and final height outcomes were evaluated along with some body composition and psychological outcomes. The Jadad quality scores of the trials ranged from 1/5 to 4/5.

No existing economic evaluations were found, nor were there any studies reporting appropriate measures of quality of life.

Summary of benefits

Although the quality of evidence proved variable, the studies suggest that GH treatment can increase short-term growth and improve final height. The reported effects of GH on short-term growth should be considered more reliable because the evidence is of higher quality. The effects of GH on final height should be considered with much greater caution because the quality of the studies is generally much poorer.

Results suggest that the effects of GH on short-term growth velocity (at 1 year) can range from no improvement to approximately 1 standard deviation above the normal growth velocity for children of the same age.

Final height gains for treated children over untreated children appear to range from approximately 2 to 11 cm (GHD, 8–11 cm; TS, 5 cm; CRF, 3–9 cm; PWS, 10–11 cm; ISS, 2–7 cm).

Costs

Treatment with GH is expensive. The lifetime incremental cost of treating one child with GH (as opposed to simply monitoring growth) ranges from £43,100–53,400 (for GHD) to £55,500–83,000 (for PWS). These costs, when applied to children aged 8–15 years with the analysed indications in England and Wales, result in total discounted costs of £904 million for complete treatment. The costs for treating children only in the four licensed conditions would be approximately £180 million.

Cost per centimetre gained

The available data suggest that, under base case conditions, the incremental cost per centimetre gained in final height is approximately £6000 for GHD, £16,000–17,400 for TS, £7400–24,100 for CRF, £13,500–27,200 for ISS and possibly in the region of £7030 for PWS (estimated using year 2000 prices).

Sensitivity analysis

A range of impacts of parameter values for the economic models were evaluated in sensitivity analyses. These evaluations tested length of treatment (1–13 years), final height effect (10–300% of the effect from the base case from trials), GH dose (varying by indication), GH cost (£15– 25/mg), annual range of discounting for benefit (0–6%) and annual rate of discounting costs (0–12%). The analyses confirmed the sensitivity of cost-effectiveness estimates and the most important factors (effectiveness, GH dose and costs due to the length of treatment).

Limitations of the calculations (assumptions made)

The economic evaluation is limited by the quality of the trials that provided the effectiveness data. In addition, these trials may not be generalisable to current treatment programs because even those that continued to final height generally started with relatively old children and treated them for a relatively short time (approximately 5–8 years). These factors were evaluated in the sensitivity analyses, but which combinations of conditions could actually exist needs careful consideration.

Conclusions

Implications

GH is already prescribed in the UK. However, a full course of treatment is expensive. Given that only a minority of children with licensed conditions are currently receiving GH, the budgetary impact of large increases in prescribing would be substantial. If GH were to be prescribed to any significant proportion of children with ISS, the budgetary impact would be very substantial because this group of children is much larger than the others.

Need for further research

Large, multicentre RCTs are needed. These RCTs should focus on final height, which is the best outcome for assessing the effectiveness of GH, and should address quality-of-life factors for use in economic modelling.

Chapter 1

Aim and background

Aim of the review

The aim of this report is to provide a rapid and systematic review of the clinical effectiveness and cost-effectiveness of growth hormone (GH) in children with one of five conditions: growth hormone deficiency (GHD), Turner syndrome (TS), chronic renal failure (CRF), Prader–Willi syndrome (PWS) or idiopathic short stature (ISS).

Description of underlying health problem

This review includes the assessment of the use of GH in five different conditions (GHD, TS, CRF, PWS and ISS) that vary in aetiology and in morbidity. Therefore, each condition is treated in a separate section that includes a description of the underlying health problem and current service provision, as well as an overview of the effectiveness of GH and the adverse events reported in trials of GH as therapy for that condition. Each section also includes an evaluation of the cost-effectiveness of using GH to treat that condition.

In all five conditions, a primary concern is that the patients affected are of unusually short stature. This short stature can have any of several origins. The current report focuses on GH treatment of short stature arising from the five conditions specified above. GH is licensed for use in the treatment of GHD, TS, CRF and PWS. The use of GH for treating ISS is not licensed.

Height varies naturally within a population, and therefore an individual's height generally is measured relative to population norms for sex and age. In addition, different subgroups of people (e.g. living in different geographic regions) will have somewhat different population distributions for height. Certain medical conditions can affect height such that the distribution of heights for individuals with those conditions is shifted relative to the normal distribution. *Figure 1* shows a normal distribution.

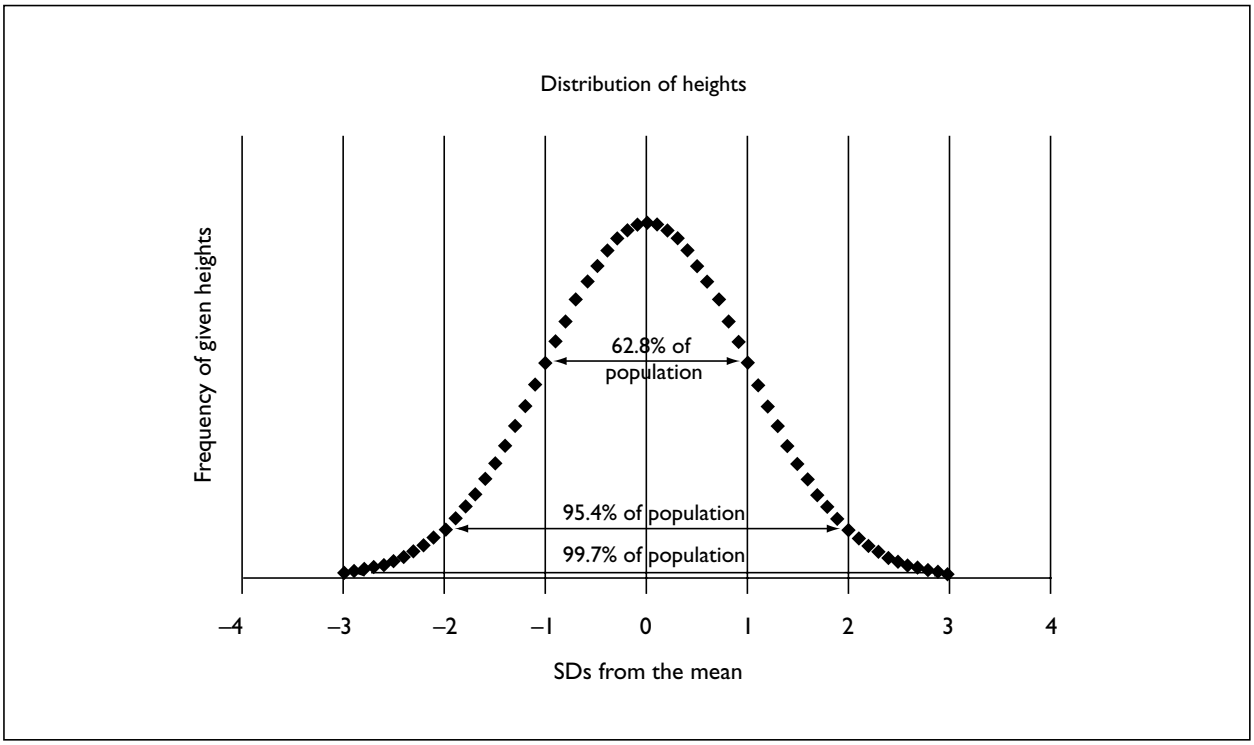

FIGURE 1 *Normal distribution of heights (Note: Short stature is sometimes defined as height below the 3rd percentile, which is 1.88 standard deviations [SDs] shorter than the mean, while the 97th percentile is 1.88 SDs taller than the mean)*

TABLE 1 *Approximate untreated adult heights (cm) for normal adults and adults with the conditions being considered*[*]

Approximate untreated adult heights (cm)	–2 SD	Mean	+2 SD
Normal men[1]	**164**	**178**	**191**
Men with GHD[†2]		134–146	
Men with CRF[‡3,4]		156[§]	
Men with PWS[5]		154	
Men with ISS[6]		157–170	
Normal women[1]	**152**	**164**	**176**
Women with GHD[†2]		128–134	
Women with CRF[‡3,4]		152[§]	
TS[7] (all women)	129	143	157
Women with PWS[5]		145–149	
Women with ISS[6]		137–156	

[*] *When SDs for final adult heights are converted to centimetres, the normal distribution cited here was used for the conversion:*
1 SD in normal adult male height is approximately 6.7 cm, and 1 SD in normal adult female height is approximately 5.96 cm
The values cited in the table are rounded
[†] *GHD is not knowingly left untreated, therefore estimates were based on very small groups of patients*
[‡] *Estimate was based on a small group of patients who were relatively old at the start of renal therapy*
[§] *Height of children with congenital CRF at age 10 years was –2.37 SD*

Table 1 shows estimates of the associated heights in centimetres for normal adults and for untreated adults with the five conditions being considered in the review.[1–7] This table provides an overview of the degree to which these conditions affect adult height.

There will always be a distribution of heights across individuals, meaning that there will always be individuals who are very short or very tall relative to their peers, independent of how the mean of the distribution(s) may change.

A child's height relative to their age can be reported relative to their chronological age or to their bone age (a measure of skeletal maturity). Because for children the salient comparison would be their height relative to other children of the same chronological age, the standard deviation scores (SDS) reported here are all relative to chronological age, unless specified otherwise. In addition, the term 'age' will always be used to specify chronological age.

Incidence and prevalence

In order to easily assess the magnitude of potential GH treatment across the conditions, incidence and prevalence for the five conditions are summarised here.

Table 2 shows estimates of the number of children who are diagnosed with the conditions of interest and estimates of the extent of GH treatment. Further details are provided in appendix 1. The table demonstrates that a minority of the children who might receive GH are currently being treated. According to a recent audit of GH prescriptions in the UK, approximately 2000 children aged under 16 years in England and Wales were receiving GH.[8] Thus, approximately 7% of those children who might be treated are receiving GH. The proportion of children with licensed indications who are currently receiving treatment is approximately 26%. Although virtually all children with some indications (e.g. GHD or TS) might eventually be treated, in other indications (e.g. renal disease) a proportion of children are not particularly short or might not opt for treatment. An estimate of the maximum number of children with licensed indications who might be treated is also included in *Table 2*. It should be noted that GH was not licensed for use in PWS at the time of the audit.

The prescription audit may have underestimated the number of current prescriptions for GH, particularly among children with renal disease because prescriptions issued by nephrologists may have been missed. In addition, the survey was conducted as of October 1998. More children may have been placed on GH treatment in the last several years since the audit. However, these estimates are likely to be reasonably accurate, because all the clinical members of the British Society for Paediatric Endocrinology and Diabetes (BSPED) were surveyed and asked to identify other clinicians prescribing GH.

Description of the intervention

Recombinant human GH has been available since 1985, shortly after GH from cadaveric human pituitaries was withdrawn from use because of its association with the transmission of Creutzfeldt–Jakob disease. Recombinant human GH (somatropin) is available as five preparations on the UK market: Genotropin® (Pharmacia Laboratories Ltd, Milton Keynes, UK), Humatrope® (Eli Lilly and Co Ltd, Basingstoke,

TABLE 2 *Estimated incidence, prevalence and treatment patterns for each of the considered conditions (see appendix 1 for further details)*

Condition	Incidence		Prevalence (age < 16 years)		Estimated number (%) of patients currently treated with GH in England and Wales	Estimated maximum number (%) of patients treated with GH for licensed indications
	England	Wales	England	Wales		
GHD	120	7	2,726	162	1,150 (40%)	2,888 (100%)
TS	117	6	1,872	96	391 (20%)	1,870 (95%)
CRF	86	5	607	36	56 (9%)	514 (80%)
PWS	32	2	512	32		490 (90%)
ISS	1,325	78	21,204	1,254	< 275 (1.2%)	
Total			28,501		1,872 (6.5%)	5,634

UK), Norditropin® (Novo Nordisk Ltd, Crawley, UK), Saizen® (Serono Pharmaceuticals Ltd, Feltham, UK) and Zomacton® (Ferring Pharmaceuticals Ltd, Langley, UK). Each product is produced by recombinant DNA technology and has a sequence identical to that of human GH.

GH therapy is contraindicated in cases of tumour activity and should not be used after renal transplant in seriously ill children or for growth promotion in children with closed epiphyses. Side-effects can include headache, visual problems, nausea and vomiting, fluid retention (peripheral oedema), arthralgia, myalgia, paraesthesia, antibody formation, hypothyroidism and reactions at injection site. Chapter 9 provides a more complete overview of adverse effects.

The 1998 prescription audit[8] revealed relatively uniform prescribing practice throughout the UK, relatively low levels of prescription beyond licensed indications (22%) and stable patterns of prescribing practice over the previous 2 years.

GH is prescribed in association with a paediatric endocrinologist or a general paediatrician with a special interest in endocrinology. It is prescribed in milligrams or international units (IU) according to body weight or body surface area and is self-administered (or given by the parent) at home, usually as a subcutaneous injection, generally 6–7 times per week. To more closely approximate the natural fluctuations in GH, the injections are usually given at night.

Routine follow-up should be performed by a paediatric endocrinologist in partnership with the general paediatrician and/or the general practitioner (GP) to assess the response to GH treatment. Treatment dose will need to be amended as the patient grows and at puberty. A shared care protocol detailing treatment has been produced by BSPED.

GH is generally prescribed for a number of years – from the diagnosis of the growth deficit until growth is complete. For an individual child, how long this would be depends upon whether the condition is present from birth (e.g. TS) or acquired later in childhood (e.g. due to tumour and irradiation, or CRF). Most trials of GH have been of relatively short duration (e.g. 5 years), but in practice in many children, therapy could continue for as long as 12 years or more. Expert opinion is that GH therapy is generally not started before age 4 years.

GH can be given as replacement therapy (i.e. a physiological dose as in GHD), in which it is intended to supplement low levels of naturally occurring GH in order to achieve normal levels. In other conditions, GH is given at supraphysiological levels – levels considerably higher than normal. The logic in administering supraphysiological doses is generally that children who have growth deficiencies, but not a hormone deficiency, have some lack of sensitivity to the hormone.

The recent convention has been to express doses in milligrams, which therefore will be used in this report to express all doses (3 IU = 1 mg). Doses computed by weight are not easily converted into dose by surface area and vice versa, because the conversion depends upon a child's weight relative to their height. Therefore, doses are reported here in the units in which the study prescribed GH. Finally, most studies report the GH dose in units per week. Therefore, all doses in the text are stated in dose per week (assuming seven doses per week when dose per day was reported). The original description of doses (both in units and time period) is included in the data extraction tables found in the appendices.

Chapter 2
Methods

The *a priori* methods are described in the research protocol (appendix 2). Further detail and clarifications to the protocol are described in this chapter. The information sources used are outlined in appendix 3.

Methods for evaluating studies

Inclusion and exclusion criteria

As described in the protocol, studies were included if they tested the effects of GH in children with one of the five conditions of interest. Outcomes focused on those clinically relevant to children with growth deficiencies. Quality-of-life measures were also reported when available in the context of randomised controlled trials (RCTs). These measures could include psychological and cognitive outcomes.

The key outcome measure of final height is rarely obtained from RCTs, and therefore it was necessary to move down the hierarchy of evidence to find the best non-randomised studies reporting final height. This was done by searching for studies that reported final height and included a separate control group. No studies with an appropriate control group were found in relation to GHD because it is not considered ethical to leave GHD untreated. Therefore, studies that reported before- and after-treatment results from large groups of children with GHD were also included. To maximise the generalisability of these results, only studies with a sample larger than 300 patients were included. Similarly, no studies that reported final height in PWS and that had a control group were found. Only one study reporting final height in PWS was found. Despite the lack of a control group and a small number of participants, this study was included because there were no other final height data. For the remaining three conditions, studies were not included if they reported final height data but did not use a comparable control group of children not treated with GH. Therefore, open non-randomised trials, prospective non-randomised trials with concurrent controls, prospective non-randomised trials with historical controls and retrospective non-randomised trials with concurrent controls were potentially included for final height data, with only the highest level of evidence reported within each condition.[9]

In addition, only data from controlled aspects of studies (or final height data as described above) were evaluated and discussed. For instance, some of the included studies began with a controlled phase and in later phases treated all participants with GH. Because there is no comparison available in these later phases, data from the later phases were not evaluated.

It was suggested that RCTs comparing GH with other treatments should be included in the review. This was considered inappropriate because explanatory trials of GH versus placebo/no treatment are the best evidence to answer the question of clinical effectiveness of GH. Also, GH is standard treatment, so head-to-head studies with other treatments would not be relevant.

Studies identified by the search strategy were assessed for inclusion through three stages (see *Figure 2* in chapter 3).

Additional inclusion criteria for economic evaluations were that studies must:

- be published
- be available in full (i.e. excluding abstracts) to enable adequate quality assessment because, within the scope of this review, it was not possible to contact authors for further details
- include a comparator (or placebo)
- include both the costs and consequences (outcomes).

Data extraction and quality assessment

Methods for data extraction and quality assessment are described in appendix 2. The quality of included RCTs was judged using Jadad criteria (appendix 4),[10] and non-RCTs were judged using modified Spitzer criteria (appendix 5).[11]

Methods of analysis/synthesis

The clinical effectiveness of human GH in children was synthesised through a narrative review with full tabulation of results of all included studies. Meta-analyses using the Cochrane Review Manager software were not considered practical

and appropriate because of the heterogeneity of studies.

The review includes a Quality of Reporting of Meta-analyses (QUOROM)-style flowchart of trials searched for and included (see *Figure 2* in chapter 3).

Observations and insights on starting/stopping rules for treatment and optimal treatment strategies identified from the included clinical effectiveness studies are reported (see chapter 10).

Methods of economic analysis

Approach

The cost-effectiveness of GH treatment for children was separately assessed for each of the five conditions of interest. The approach adopted was first to identify, synthesise and critique the existing published economic evaluation evidence and then, depending on these findings, to estimate the impact on the NHS and Personal Social Services sectors in England and Wales. It was anticipated that to do this would require either adapting existing cost-effectiveness models if they existed, or if they did not exist or were inappropriate, building a cost-effectiveness model for each condition by synthesising the best available economic and effectiveness evidence along with current epidemiological data and patterns of service use that would be applicable for England and Wales.

A key question to be addressed when building or assessing a cost-effectiveness model is the appropriateness of the outcome measures. In this case, the primary objectives of GH treatment are recognised as normalisation of height during childhood and attainment of normal adult height. Consequently, the most robust clinical effectiveness measure used in studies is final height. Other more intermediary measures used include height achieved for the length of treatment (not necessarily until the end of growth), growth velocity (GV) and height standard deviation score (HtSDS). However, GH treatment may also have an important direct impact on patients' quality of life, at least for some subgroups of patients. For example, evidence has shown that GH treatment may improve energy levels for children suffering from GHD or PWS, and may impact on a number of general quality-of-life dimensions for all treated conditions. The main ones studied include behaviour, intelligence, educational and professional attainment, social competence, anxiety and depression. Thus, an important question was to answer whether there were clear, unambiguous and measurable quality-of-life effects, relating to some or all conditions treated, that ought to be included in any final measure of outcome to reflect more accurately the full economic benefits of GH therapy. To answer this question, a systematic rapid review was also undertaken for studies of quality of life and other benefits relating to GH treatment for the conditions listed.

Sources of information needed to inform economic modelling are broader than for an initial rapid review of the economic evaluation evidence. Thus, it was a requirement to supplement the primary literature search and review with additional studies on resource use, costs and benefits that, although not economic evaluations, were considered useful components for populating the cost-effectiveness models.

Literature review

A broad search strategy was used to identify economic evaluations, costs, quality-of-life and utility studies (see appendix 3). The literature reviews were carried out from an NHS and Personal Social Services perspective regarding costs and from the societal (children/parents/carers) perspective regarding benefits.

The search yielded one possible economic evaluation and no cost studies. The Development and Evaluation Committee (DEC) report into *Growth hormone in children*[12] reported cost per quality-adjusted life-year (QALY) for GHD (£5,700–20,800 per QALY), and for TS, CRF and ISS (£11,400–41,700 per QALY). The measures of benefit used are problematical because no primary studies were available to inform the relationship between the degree of height gain and psychological benefits gained from treatment. Instead, calculations of 'best'- and 'worst'-case scenarios were used, but these were based on unjustified guesses about the starting and finishing health states for such children receiving treatment. Consequently, these results are not sufficiently robust to inform modelling.

The search also identified 15 studies on the quality-of-life effects of short stature in children and in GH-treated children with short stature. It is important to note that the search was intended to identify possible economic quality-of-life measures and therefore is not a comprehensive search on quality-of-life measures. One RCT assessed the psychological effects of GH treatment in patients with TS[13] (see chapter 5). The remainder were of lower-quality evidence and included:

four studies that considered quality-of-life effects for children with ISS, two studies that considered mixed patient populations, three studies that considered the effects of treatment in children with GHD, three studies on patients with TS and one study on children with CRF. Another two studies explored the economic benefits of GH treatment, based on parents' valuations. A list of these references can be found in appendix 6. Data extraction for these studies is available on request.

The main problems experienced in trying to summarise the quality-of-life studies were that many different quality-of-life measures were used to assess the different domains of quality of life and that different effects could be expected depending upon the condition. In addition, studies of different conditions may have considered other outcome measures (appendix 7). For example, GH treatment may affect energy level, body mass index (BMI) or body fat, as well as height and quality of life. Equally problematical for trying to summarise the studies was that very often no clear justification was given for the use of particular quality-of-life measures; most studies lacked suitable control groups and frequently employed hospital-based samples. As a result, interpretation of individual studies, comparability across studies and validity of estimates were significantly compromised. One clear finding was that the value of height gain affected children of different ages differently, and so it would be incorrect to assume that any benefit occurring over childhood and adulthood would be uniform. It should be noted that no quality-of-life studies were found for GH treatment in children with PWS.

Two exploratory studies of the value of GH treatment were identified but, unfortunately, had little relevance to this review. One used the technique of conjoint analysis to investigate the value of individual attributes of GH treatment (i.e. amount and certainty of the effects, and side-effects), based on the views of parents of potential beneficiaries.[14] The study findings did not generalise to the UK because the study was conducted within a US health system. The second study, from the UK,[15] directly estimated parents' willingness to pay for GH treatment for their children. The study could only indicate parent's value of benefits, saying nothing about associated costs or societal benefits. Therefore, the study has little direct relevance for assessing the cost-effectiveness of treatment from the point of view of the NHS and Personal Social Services. Despite these limitations, both studies showed that study participants placed a high value on GH treatment.

Cost-effectiveness modelling

As the literature review identified only one cost–utility study, which was inadequate, there were no suitable economic evaluation models available to be re-evaluated. Clearly, cost–utility analysis would have been the preferred technique for modelling, and because of this, the possibility of generating informed approximations for QALY weights for treated and untreated patients was considered, with help from the Turner Syndrome Support Society (TSSS). Two problems were encountered: (1) no suitably sensitive quality-of-life instrument was available to use that had been validated for use with children or parents/guardians and that would yield a single utility value, and (2) controlling for background factors within the TSSS membership was found, on closer inspection, to be too big a task. Full details are reported in appendix 8. Consequently, separate cost-effectiveness models were built for each condition (GHD, TS, CRF, PWS and ISS).

Models typically use observed and modelled epidemiological, cost and treatment effectiveness data from multiple secondary sources to build a coherent analysis. It is usual to derive these data from published studies, routine reports and activity data, and experts' judgement to formulate a range of reasonable estimates, depending on what is available and most relevant. The models may also make use of a series of assumptions and educated guesses by the modeller if better data are not available. Inevitably, the biggest drawback of these models is that they can be prone to biases. A good model requires relevant structure, data and extrapolation methods, transparency and extensive testing for robustness using appropriate sensitivity analyses. An advantage of modelling is that it is possible to adjust a model if more suitable data become available, but it is much harder to adjust a structurally flawed model or one that is poorly reported. Full access to the model is necessary to update or adjust it to suit local or national requirements.

Modelling approach

For each condition, comparison was made between GH treatment and no GH treatment. No GH treatment is defined as growth monitoring. In many parts of England and Wales, growth monitoring is the usual practice followed when GH treatment is not prescribed for children of short stature presenting to the specialist. For comparability between the two alternatives, the same period of childhood growth was assessed, although the period could vary under different scenarios.

Recurrent costs were assessed from the perspective of the English and Welsh NHS and Personal Social Services sectors. Future costs were discounted and presented in year 2000 prices.

Findings of clinical effectiveness within each condition were used to determine estimates of effect size best suited for the cost-effectiveness modelling. Outcomes were assessed from the patients' perspective (final height for children with GHD, CRF, TS, ISS and PWS, and 1-year improvement of HtSDS for children with PWS). These outcomes were considered the best measures available. For each condition, a number of clinical studies were reviewed, and evidence from only the least biased studies was incorporated. The cost-effectiveness models required, whenever possible, RCT evidence, use of final height as the primary outcome measure and data reported as mean effect size. If this was not possible, then lower-quality evidence was used.

There was no good evidence to suggest GH treatment has significant adverse effects on any condition treated, nor costs associated with treating adverse effects. Therefore, this aspect was not incorporated into the models but could be if evidence was to be made available at a later date.

The incremental cost-effectiveness ratio (ICER) (i.e. the payoff from treatment) is presented as an expected (discounted) incremental mean cost per centimetre of final height gained for children with GHD, CRF, TS, ISS and PWS, and expected (discounted) incremental mean cost per unit HtSDS improvement at 1 year for children with PWS. Careful interpretation of ICERs is needed, particularly because of difficulties finding a suitable unit of effect. While mean difference in final height is considered a key outcome measure for assessing efficacy of GH treatment, incremental effectiveness measured by this method is unable to discriminate between the amount of height gained relative to current height and across individuals. The assumptions built in are that a centimetre gain is achieved by each patient treated and worth the same to all beneficiaries. Of course, it would be possible to use other units of height gain that might at first glance appear more clinically meaningful, for example, a large actual or percentage gain, but the problem is that these units may not be achievable in some individual patients, and therefore some patients are likely to benefit more from treatment than others.

Each model built used a similar, simple deterministic decision tree approach, populated with the best evidence or assumptions available at the time of the review. The full models were constructed and analysed using Excel™ 2000 software and are available in electronic format.

Event pathways

Expected event pathways for each condition (treated and not treated) were modelled using typical diagnostic and treatment pathways (see appendix 9). These pathways were obtained from two sources: the BSPED consensus statement on diagnosing and treating children with GHD[16] and clinical expertise from a local NHS consultant in paediatrics and endocrinology (Southampton General Hospital) to advise on similarities and differences for remaining conditions.

With help from experts (the consultant in paediatrics and endocrinology, and a paediatric endocrine specialist nurse), pathways were used to identify and quantify resource items (i.e. the different types and quantities of healthcare contacts, tests, procedures and drug regimens used for each treatment alternative).

If children with short stature are referred to a specialist paediatrician/endocrinologist and no GH treatment is recommended, patients will usually be monitored twice yearly during the growth period. If GH treatment is to be considered in patients suspected of having GHD or ISS, they undergo investigation to determine their GH status. This investigation typically involves blood and urine tests during an initial outpatient visit, and if GHD is suspected, a day's hospital admission allows further investigation using the GH provocation test. If an abnormal reading occurs on a first test, the patient is given a second test. All patients with two subnormal peak readings of GH on provocation tests have a magnetic resonance imaging (MRI) scan and skull X-ray to confirm GHD. A positive diagnosis of GHD means the patient is offered GH treatment that, if accepted, will be provided in three phases over the period of childhood growth. The first year of treatment includes the training of parents and patients in the administration of the daily injections, drug therapy and monitoring. The second year and subsequent annual treatment until growth has ceased include monitoring (a repeat of the tests carried out during the investigation) and adjustment of drug dose during the years of puberty. Finally, there is a year of follow-up care at the end of treatment. For each phase, different types/mixes of healthcare contacts are encountered.

Patients with TS, PWS or CRF who are referred to the paediatric endocrinology specialist follow similar pathways. The main differences in the diagnostic and treatment pathways relate to: drug dose (given according to patient weight, with larger doses used for ISS, TS, CRF and PWS), the practice of diagnostic testing (some of the patients with GHD could require regular monitoring of pituitary function) and follow-up care for patients with GHD (provocation tests are performed at the end of treatment to check whether the patients still have GHD). Modelling incorporates current recommendations for drug doses for each condition and uses the literature to estimate average length of treatment. The estimate of costs and effects is modelled for each condition by using two base cases (base case 1 and base case 2) alongside a series of scenarios and one-way sensitivity analyses. In each case, the base cases provide an informed indication of effect size, drug doses used and duration of GH treatment, because these parameters are likely to have the biggest impact on cost-effectiveness. The choice of two base cases aims to provide the range of variability of the cost-effectiveness estimates. The two effectiveness studies used for the GHD and CRF models are the only ones reporting final height from the studies identified in the review. The two effectiveness studies used for the TS model reflect the best-quality evidence available. The two effectiveness studies for each of the remaining conditions were selected to provide a range from 'better' to 'worse' effect size. Because there was uncertainty surrounding the choice of parameters to use in the cost-effectiveness models, scenario and sensitivity analyses have been conducted. The scenarios describe key combinations of factors influencing successful treatment and cost of treatment relevant to each condition, and sensitivity analysis evaluates the individual impact of key parameters by assessing the impact of minimum and maximum values. Scenario results relating to all five conditions are presented in the main text, and sensitivity analyses relating to the ICERs of all five conditions are presented in appendix 10.

The decision tree modelling of cost-effectiveness of GH replacement needs data about effectiveness, resource use and costs. *Table 3* describes the model parameters that were common to all five conditions, the values associated with each and the source of these values.[17–22] When there were ambiguous criteria or data to inform the modelling process, a base case value was established. Whenever possible, values were selected to represent usual UK practice conditions.

Further clarification of model assumptions and definitions

The list below clarifies some of the main model assumptions and definitions.

1. The most appropriate long-term clinical effectiveness measure identified for GH treatment in children was final height. This measure could be reported for GHD, ISS, CRF and TS, but the best available evidence for PWS was 1-year HtSDS. It is harder to put a meaningful interpretation on the latter, and results for PWS cannot be compared with the other conditions.
2. All clinical studies used to estimate effect size are reported for participants completing GH treatment and could not be adjusted for intention-to-treat analysis. Estimates of effectiveness assumed no difference in the effectiveness between drop-outs from GH treatment at 1 year and monitored patients.
3. The unit of incremental effectiveness takes into account mean unit effectiveness difference between a treated and non-treated patient after adjusting for sex and proportion of drop-outs (when data are provided). It was assumed that those patients who dropped out in the first year will not gain additional final height, while those who continued treatment will have a mean increase in final height, as suggested by the study results. It is not known with certainty what proportion of patients will drop out of treatment. Using rates from clinical trials data, the starting point was to assume all treatment drop-outs occur at the end of the first year of treatment. But expert advice suggested these rates were likely to overestimate the situation, and a scenario for each condition replaced this assumption with 0%, 10% and 20% drop-out rates.
4. Average age at the start of GH treatment was defined as the usual age at the end of growth monitoring minus current average length of GH treatment minus the average time from the end of GH treatment to the end of growth monitoring (inferred from trials).
5. The data on the average length of treatment were taken from the studies providing the effectiveness data. A scenario for different lengths of treatment informs on the impact of this parameter on costs.
6. Possible acceleration of puberty due to GH treatment was not taken into account.
7. The drug doses incorporated were based on the data from the studies providing the effectiveness data. A sensitivity analysis for recommended drug doses of treatment informs on the cost impact of this parameter. Although

TABLE 3 *Common parameters of cost-effectiveness models*

Parameter	Value and source
Population data	
Weight/age distributions by sex	Boys four-in-one growth charts, UK cross-sectional reference data: 1996/1[17] Girls growth chart, UK cross-sectional reference data: 1996/1[18]
Weight	50th percentile for sex and age
Effectiveness data	
Final height	Values from relevant sections of this report
Investigation and treatment parameters	
End of growth-monitoring age	Assumed to coincide with the end of puberty at age 17 years (expert opinion)
Cost data	
GH drug cost (Genotropin, Humatrope, Norditropin, Saizen, Zomacton) per mg	£20.82 (£20.82–23.42[19])
Outpatient visit to paediatric department	£97 per visit[20]
Day admission to paediatric department	£126 per day[20]
G grade district nurse	£33 per hour[20] for E grade, adjusted based on midpoint differences at Southampton University Hospitals Trust
X-ray, hand (bone age test)	£12 per test[21]
X-ray, skull	£22 per test[21]
MRI, skull	£126 per procedure[21]
Blood test (for full blood count, chemical profile, thyroid and IGF)	£20[21]
Urine test	£4[21]
GH provocation test (glucagon/clonidine/other)	£292 (an additional nurse for 8 hours plus eight blood tests)
Investigation of other pituitary hormones	£345 (a day admission plus an additional nurse for 6 hours and six blood tests)
Discounting	
Discounting rate, cost	6.0% (NICE)[22]
Discounting rate, benefits	1.5% (NICE)[22]

IGF, insulin-like growth factor; NICE, National Institute for Clinical Excellence

some evidence suggests these doses may be important for the effectiveness as well, it is overall not robust enough to represent formal quantitative relationships in these models.

8. In cases in which study results were presented separately for boys and girls, the sex distribution for the condition was used to calculate the mean incremental final height per person in the condition.
9. Effectiveness data were discounted at 1.5% per annum for the average length of treatment, assuming effects accumulate uniformly throughout treatment.
10. Estimates for drug dose were calculated for age- and sex-related 50th percentile weight, but alternatives using the 9th weight percentile in scenarios relating to GHD, ISS, CRF and TS as well as the 25th weight percentile for TS were also assessed. The drug dose used for GH treatment in children with GHD is that recommended by BSPED: a range between 0.175 and 0.35 mg/kg/week.[16]
11. The minimum *BNF* price listed for somatropin brands of £20.82/mg was used in base cases 1 and 2.[19]
12. Although shared care arrangements between specialists and GPs operate in most parts of England and Wales, GH treatment monitoring was assumed to take place in a secondary care setting so that all monitoring costs were covered by hospital activity.
13. The patient's GP or specialist can prescribe GH. Once again, this practice varies across England and Wales. In the case of a hospital consultant issuing GH prescriptions, value-added tax (VAT) is payable in addition to the GH price. In general, the hospitals are reluctant to fund GH treatment. A direct home-delivery arrangement could be set

up in order to avoid VAT payment by hospitals, but delivery charges are payable in these cases. Due to the lack of reliable data on the arrangements across the country, it was decided to incorporate *BNF* prices without adding VAT.

14. When it was not possible to use generalisable costs (i.e. for the costs of diagnostic procedures), local health service costs were used. This may bias cost estimates but can be easily substituted if, and when, data that are more reliable become available.
15. It is most likely that treatment pathways and hence patterns of healthcare resource use vary across the UK, but because no data were available to describe the extent of these variations, they could not be adequately represented in the models.
16. The cost analyses incorporate the effect of discontinuing treatment but not the impact of compliance with appropriate dose of daily injections by individual patients or wastage that could arise from the expiry of GH if too much was bought at one time.

Chapter 3
Included studies

The process of including studies for the assessment of effectiveness is shown in *Figure 2*.

A list of studies excluded from the assessment of effectiveness can be found in appendix 6. The primary reason for excluding studies was that they did not include a placebo control or a group not receiving treatment. Although many of these studies were RCTs, the lack of a placebo control or no-treatment group means they are not informative about the effectiveness of GH *per se*. In the case of GHD, studies without a control group were included because it has been considered unethical to include control groups in this condition. Some publications were also excluded because they reported on subsets of patients who were described in another publication or they were follow-ups to other publications that were included (some of these were longer-term follow-ups but did not maintain the control group).

The studies listed in *Table 4* were selected by the methods described in chapter 2 and appendix 2.[23–54] They were judged to provide the highest-quality information available as to the effectiveness of GH within each condition.

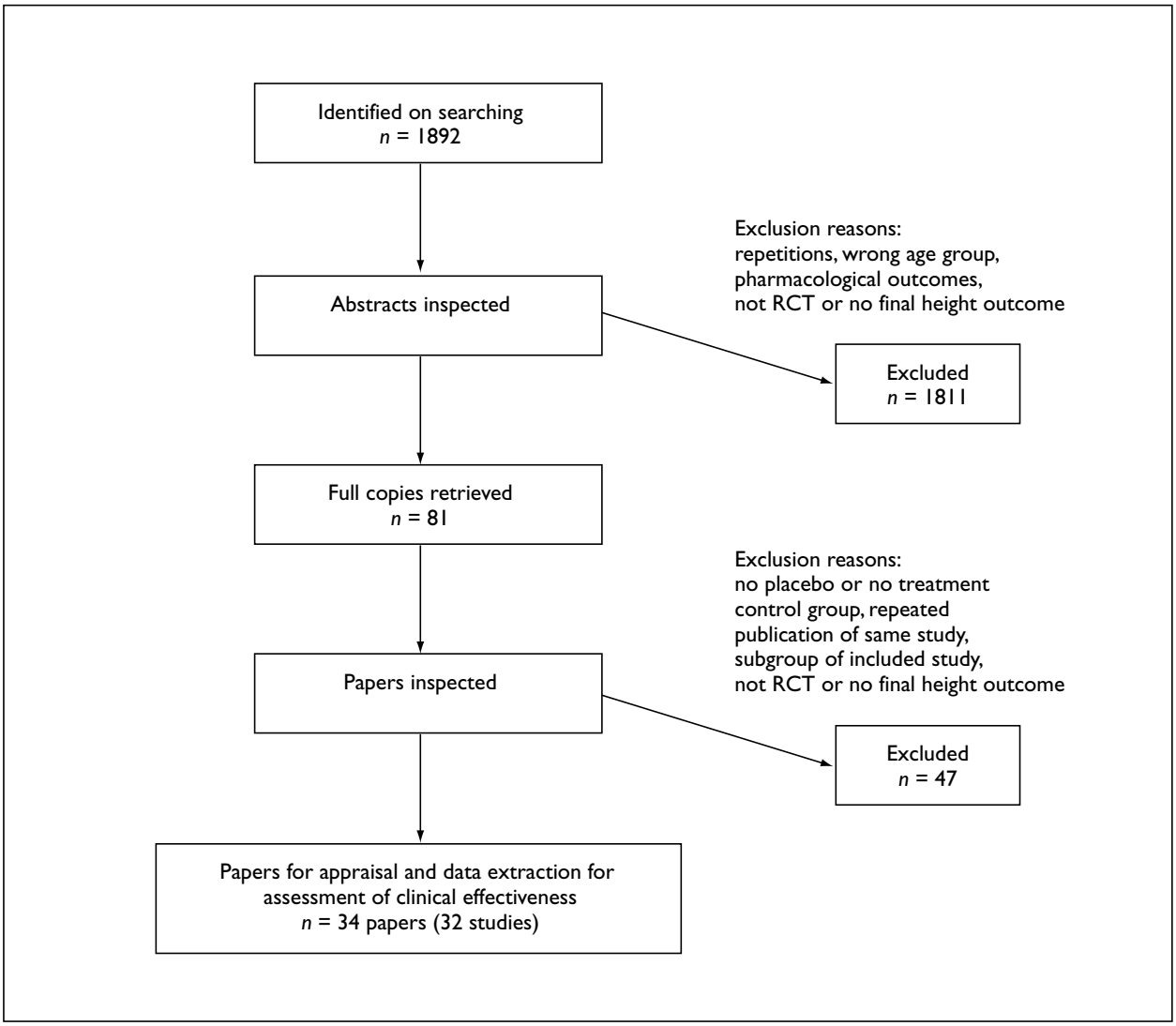

FIGURE 2 *Flowchart of identification and inclusion of effectiveness studies (RCTs and studies of final height) from the initial search*

TABLE 4 *List of studies included in assessment of effectiveness*

Included studies (all are published studies)	Condition	Number of patients	Outcomes considered			
			Final height	HtSDS	GV	Other
RCTs						
Soliman & Abdul-Khadir, 1996[23]	GHD and ISS	53 (GHD) 24 (ISS)		✔	✔	
CGHAC, 1998[24]	TS	69	✔	✔		
Rosenfeld, 1990[25] and 1989[26]	TS	35			✔	
Rovet & Holland, 1993[13]	TS	95				Psychological
Ross *et al.*, 1997[27]	TS	40				Cognitive
Fine *et al.*, 1994[28]	CRF	125		✔	✔	
Powell *et al.*, 1997[29]	CRF	44		✔	✔	
Hokken-Koelega *et al.*, 1991[30]	CRF	16			✔	
Broyer, 1996[31]	CRF (post-transplant)	203		✔	✔	
Hokken-Koelega *et al.*, 1996[32]	CRF (post-transplant)	11			✔	
Carrel *et al.,* 1999[33]	PWS	54		✔	✔	Body composition
Lindgren *et al.*, 1997[34] and 1998[35]	PWS	27		✔	✔	Body composition
Hauffa, 1997[5]	PWS	16		✔	✔	
Whitman *et al.*, 2000[36]	PWS	54				Psychological
McCaughey *et al.*, 1998[37]	ISS	40	NFH	✔	✔	
Genentech Collaborative Study Group, 1989[38]	ISS	121			✔	
McCaughey *et al.*, 1994[39]	ISS	41		✔	✔	
Barton *et al.*, 1995[40]	ISS	20		✔	✔	
Volta *et al.*, 1993[41]	ISS	12		✔	✔	
Cowell, 1990[42]	ISS	77			✔	
Ackland *et al.*, 1990[43]	ISS	61			✔	
Non-RCTs						
Cutfield *et al.*, 1999[44]	GHD	369	✔			
August *et al.*, 1998[45]	GHD	674	NAH			
Dacou-Voutetakis *et al.*, 1998[46]	TS	62	✔			
Hochberg & Zadik, 1999[47]	TS	49	✔			
Pasquino *et al.*, 1996[48]	TS	36	✔			
Taback *et al.*, 1996[49]	TS	31	✔			
Haffner *et al.*, 2000[50]	CRF	88	✔			
Janssen *et al.*, 1997[51]	CRF	31	✔			
Angulo *et al.*, 2000[52]	PWS	16	✔			
Zadik *et al.*, 1992[53]	ISS	28	✔			
Hindmarsh & Brook, 1996[54]	ISS	26	✔			

CGHAC, Canadian Growth Hormone Advisory Committee; NFH, near final height; NAH, near adult height

Various outcomes were extracted from the included studies. These outcomes were judged to be salient to the children themselves and to be relevant to an evaluation of the effectiveness of GH – primarily short-term and long-term growth outcomes. Outcome measures are described in more detail in appendix 7.

Chapter 4

GH in growth hormone deficiency

Background

Among children who are of very short stature (i.e. –3 standard deviations [SD] below the mean), approximately 25% have GHD. GHD includes a group of different pathologies, all with a failure of or reduction in GH secretion. GHD may occur by itself or in combination with other pituitary hormone deficiencies. It may be congenital or acquired as a result of trauma, infiltrations, tumour or radiation therapy. Despite the large number of possible aetiologies, in the past most children had idiopathic GHD, but now many cases of GHD result from pituitary or hypothalamic tumours, or following radiotherapy (used to treat children with brain tumours or given as prophylaxis in patients with leukaemia).

Typical features of a GH-deficient child include short stature, decreased GV, immature facial appearance and increased subcutaneous fat mass.[55] The degree of short stature can range from mild to very severe, depending on the degree of deficiency, the age of onset and parental heights. Suggested clinical criteria for diagnosing GHD include:

1. severe growth retardation with HtSDS for chronological age less than 3 SDS below the mean
2. moderate growth retardation with HtSDS for chronological age between 2 and 3 SDS below the mean and decreased growth rate (GV below 25th percentile for age)
3. severe deceleration in growth rate (GV below 5th percentile for age)
4. decreasing growth rate combined with a predisposing condition such as previous cranial irradiation
5. evidence of other pituitary hormone deficiencies or signs of congenital GHD (e.g. hypoglycaemia or microphallus).

In addition, retardation of bone maturation is found in most cases.[55]

It should be noted that children with GHD generally have a very slow rate of growth such that, over time, their height falls further and further behind other children of the same age.

The diagnosis of GHD is confirmed by measurements of GH secretion, commonly in several samples following stimulation by a provocation agent such as insulin or clonidine. The definition of a normal response is still rather arbitrary but is usually set at a peak GH level of more than 20 mIU/l[56] or more than 10 µg/l.[16,57] This value has changed over time, there is a lack of normative data for GH provocation tests, and different tests have different potencies. It has been noted that this level needs to be revised downwards when using newer monoclonal-based assays and recombinant human GH reference preparations.[16]

Use of GH in GHD

GH has traditionally been used to treat children who are deficient in GH. In congenital forms, growth failure can usually be detected within the first year, but acquired insufficiency can lead to impaired growth at any time prior to maturity.[1] In the latter case, it is important to assess GV in addition to height. GHD would be suspected from the impairment in linear growth.

Recommendations for current practice in GHD are that GH should be administered on a daily basis in the range of 0.175–0.35 mg/kg/week.[16]

The recent audit[8] (*Table 2*) reported that approximately 1150 children with GHD in England and Wales are currently receiving GH.

The heterogeneity of aetiologies means that the duration of treatment will vary considerably among children with this condition, depending upon the origin of the GHD. Some individuals may acquire GHD relatively late in childhood or adolescence and require treatment for a short period, whereas others may have a deficiency from birth and be placed on treatment very early.

Quality and quantity of effectiveness studies

One RCT and two non-RCTs met the inclusion criteria (*Table 5*).[23,44,45]

TABLE 5 *Summary of study details: GHD*

Reference	Control group	Intervention	Participants	Duration
Soliman & Abdul-Khadir, 1996[23] Jadad score: 2/5	GH secretion status determined, then patients randomised	GH or no treatment Group Ia: GH, 10 mg/m^2/week* Group Ib: GH, 5 mg/m^2/week Group IIa: GH, 5 mg/m^2/week Group IIb: no treatment	Group Ia: 20 Group Ib: 14 Group IIa: 9 Group IIb: 10 ***Prepubertal patients with GHD*** Group I: GH peak, < 7 µg/l Group II: GH peak, 7–10 µg/l	1 year
Cutfield *et al.*, 1999[44]	None	GH, 0.16 mg/kg/week	369	8.1 years
August *et al.*, 1998[45]	None	GH, dose not reported	674 (boys:girls, 480:194)	Approximately 4.5 years

* *Groups designated I had GHD, and those designated II had partial GHD*

TABLE 6 *Summary of results assessing the effectiveness of GH in GHD*

Reference	Outcome (mean)	GH		Placebo or no treatment		Statistical comparison GH vs control
		After treatment	Δ	After	Δ	
RCTs						
Soliman & Abdul-Khadir, 1996[23]	HtSDS	Group Ia: –2.46 Group Ib: –1.12 Group IIa: –2.3	+0.84* +1.73* +1.1*	Group IIb: –2.8	+0.3	$p < 0.05$ for Group IIa vs IIb
	GV (cm/year)	Group Ia: 9.11 Group Ib: 8.1 Group IIa: 8.4	+5.66* +4.66* +4.75*	Group IIb: 5.7	+1.4	$p < 0.05$ for Group IIa vs IIb
Non-RCTs						
Cutfield *et al.*, 1999[44]	Final HtSDS	–1.5	+1.6	NA	NA	NA
August *et al.*, 1998[45]	Final HtSDS	Boys: –1.3 Girls: –1.6	+1.3 +1.4	NA	NA	NA

Δ, *change from baseline; NA, not applicable*

* *Within-group before/after comparison was statistically significant*

RCTs

One RCT met the inclusion criteria for the review (*Tables 5* and *6*, with details in appendix 11).[23]

This RCT was of a complicated design, and short prepubertal children were randomised after determination of their GH status. In the GH-deficient group (defined as GH peak < 7 µg/l), children were randomised to receive one of two doses of GH, either 10 mg/m^2/week or 5 mg/m^2/week, while in the partially GH-deficient group (defined as GH peak of 7–10 µg/l), children were randomised to receive 5 mg/m^2/week of GH or no treatment. Those children with normal GH response (defined as GH peak > 10 µg/l) were randomised to receive 5 mg/m^2/week of GH or no treatment, and results for this group are reported in the section of the review dealing with ISS (chapter 8).

The main outcome measures used in the RCT include HtSDS before and after treatment, and GV before and after treatment.

The Jadad quality score for the trial was 2/5. The trial is not described as double-blind and has no description of the method of randomisation.

Studies reporting final height

Two non-randomised studies reporting final height met the inclusion criteria for the review (*Tables 5* and *6*, with details in appendix 12).[44,45] In the Cutfield study,[44] participants with

idiopathic GHD had been treated for a median of 8.1 years with a median of the mean GH doses of 0.16 mg/kg/week. The median of the mean injection frequencies was 5.2 per week. The median pretreatment HtSDS was –3.1, and the median age at start was 9.8 years.

In the August study,[45] participants with idiopathic GHD had been treated for an average of approximately 4.5 years. GH dose was not reported. The mean HtSDS at enrolment for boys was –2.6 and for girls –3.0. Mean ages at enrolment were 12.7 and 11.2 years for boys and girls, respectively.

These studies,[44,45] in which patients were retrospectively evaluated from databases, included only those children with idiopathic GHD whose results may not generalise to other aetiologies. In addition, there may be sampling bias associated with entry into a database, although it seems that most children treated with GH are entered. These studies did not include any comparison group, instead reporting before and after measures of height (see appendix 7 for a discussion of outcome measures).

Assessment of effectiveness of GH in GHD

The studies suggest that GH does promote growth in GHD, especially when considering HtSDS (*Table 6*).

Short-term outcomes

HtSDS

The RCT[23] showed significant improvements in HtSDS within the subgroups treated with GH compared with pretreatment values after 1 year. With the higher GH dose, HtSDS improved from –3.3 ± 1.2 to –2.46 ± 1.26 ($p < 0.05$), and with the lower dose from –2.85 ± 1.2 to –1.12 ± 1.16 ($p < 0.05$) in GH-deficient children. In partially GH-deficient children treated with lower-dose GH, HtSDS improved from –3.4 ± 0.8 to –2.3 ± 0.45 ($p < 0.05$), which was statistically significant ($p < 0.05$) compared with untreated controls in which HtSDS changed from –3.1 ± 0.6 to –2.8 ± 0.45 (not statistically significant within-group change).

GV

After 1 year of GH therapy, GV significantly increased within the subgroups treated with GH compared with pretreatment values (within-group comparisons) and in the low-dose GH-treated group compared with untreated controls.[23] With the higher GH dose, GV increased from 3.45 ± 1.23 to 9.11 ± 2.25 ($p < 0.05$), and with the lower dose from 3.44 ± 1.27 to 8.1 ± 1.52 ($p < 0.05$) in GH-deficient children. In partially GH-deficient children treated with lower-dose GH, GV increased from 3.65 ± 1.1 to 8.4 ± 1.4 ($p < 0.05$), which was statistically significant ($p < 0.05$) compared with untreated controls, in whom GV increased from 4.3 ± 1.0 to 5.7 ± 1.8 (not statistically significant).

Final height outcomes

Final HtSDS

HtSDS was greater at final height than at the inception of treatment in the two single-cohort studies. In the Cutfield study,[44] the pretreatment HtSDS was –3.1, and the final HtSDS was –1.5. In the August study,[45] HtSDS for boys was –2.6 at enrolment and –1.3 at near adult height. For girls, the HtSDS was –3.0 at enrolment and –1.6 at near adult height. There were no statistical comparisons of height before and after treatment in these studies. Using current adult height norms and assuming that untreated children would maintain their pretreatment HtSDS at final height, the height gain due to GH treatment would be approximately 8.7–10.7 cm for boys and 7.7–9.5 cm for girls (see conversion footnote to *Table 1*).

Although the single-cohort studies did not include a comparison group, they represent the best available data on the effect of GH on final height in GHD. The use of SD measures of height provides some comparison with a normative group, and as discussed in appendix 7, a change in HtSDS is indicative of 'catch-up' growth. The best available indication of the effect of GH in GHD is the change in SD from pretreatment to final height. Normal children remain at the same SD in height relative to their peers throughout their growth. Although children with GHD may have a height within the normal range initially, as the deficiency continues they fall further and further behind in growth. If we assume that children with GHD would have a final HtSDS equal to their pretreatment HtSDS if left untreated, then this assumption is likely to represent an underestimate of the effect of GH on height. Without treatment, these individuals with GHD would likely be even shorter relative to their peers at adulthood than earlier in childhood. Nonetheless, considering the gain in height attributed to GH to be the SD difference between pretreatment and final height may be the best available measure of the effect of GH within this patient group.

Adverse effects

No serious adverse effects were reported in the included studies.

Cost-effectiveness of GH in GHD

Model parameters and data

A model of the cost-effectiveness of GH treatment in GHD was populated with the best available evidence. *Table 3* in chapter 2 lists the model parameters that were common to all five conditions. The additional parameters that were specific to GHD base cases are shown in *Table 7*.[8,16,23,44,45,58] The effect of GH on final height in children with GHD was taken from the effectiveness review above. The base cases differ only with respect to the estimate of final height gained and length of treatment. Base case 1 is based on the study that reports better effectiveness.[44] Base case 2 is based on the study that reports a more cautious estimate of clinical effectiveness.[45]

The estimates of the costs and cost-effectiveness of using GH in GHD were modelled using the parameters in *Table 7* in the context of the two base cases and in the context of four additional treatment scenarios (see *Table 8*). The scenarios describe important factors that could influence successful treatment as well as the cost of treatment and test factors that may more closely reflect current clinical practice and experience. These additional analyses aim to inform on the sensitivity of cost-effectiveness estimates to parameters for which there are no good data to incorporate in the base cases.

Costs, effects and ICERs

The costs of GH treatment and growth monitoring are based upon costs associated with the appropriate event pathway (see appendix 9). The event pathway for no GH treatment is depicted in diagram A of appendix 9. The event pathway associated with investigating GHD is depicted in diagram B, and the event pathway for the decision as to whether to offer GH treatment and whether treatment will be accepted in GHD is depicted in diagram C. Diagram E depicts the event pathway for GH treatment in GHD. These event pathways specify the various parameters that must be included in order to realistically estimate the costs associated with GH treatment and with no treatment (i.e. growth monitoring) in GHD.

Costs were estimated using the appropriate parameters specified from the event pathways and the treatment assumptions outlined in the scenarios above. *Table 9* reports estimates of mean discounted recurrent costs achieved under the assumptions of base cases 1 and 2.

Table 10 reports the ICERs modelled under the assumptions of both base cases. These ICERs reflect

TABLE 7 *Model parameters, values and data sources for GH in GHD*

Parameter	Value and source
Population data	
Sex distribution of patients	63% boys[8]
Effectiveness data	
Base case 1:	
Length of treatment (assumes child aged 9 years)	8 years[44]
Final height gain – benefit uniformly spread over treatment period	10.28 cm[44]
Base case 2:	
Length of treatment (assumes child aged 12 years)	5 years[45]
Final height gain – benefit uniformly spread over treatment period	8.58 cm[45]
Investigation and treatment parameters	
Drug doses – based on average age- and sex-related weight at 50th percentile and not adjusted during puberty	0.175 mg/kg/week (0.175–0.35 mg/kg/week[16])
Suspicion of GHD after first consultation with specialist, blood and urine tests	100% (modellers' opinion)
Provocation GH test[58]	
Sensitivity	0.8
Specificity	0.8
GH treatment drop-out rate after first year of treatment	9.3%[23]
Drop-out rate from monitoring after first year of monitoring	0%[23]

TABLE 8 *Scenarios for base cases 1 and 2: GH treatment in GHD*

Scenario	Description
Scenario A	Same parameter values as either base case, with the exception of the duration of GH treatment, which is assumed to vary between 5 and 12 years
Scenario B	Same parameter values as either base case, with the exception of the assumption about drop-out rate, which is assumed to vary between 0% and 20%
Scenario C	Same parameter values as either base case, with the exception of the administration of drug dose, which is based on age- and sex-related weight at the 9th percentile
Scenario D	Same parameter values as either base case, with the exception of the administration of drug dose, which is increased by 50% during puberty

TABLE 9 *Estimates of mean discounted recurrent costs per patient with GHD undergoing GH treatment and growth monitoring (2000 prices)*

Condition: GHD	Mean total cost of GH treatment	Mean drug cost (% of total cost)	Mean cost of growth monitoring
Base case 1	£55,712	£51,560 (93%)	£2,339
Base case 2	£44,990	£41,521 (92%)	£1,904

TABLE 10 *Estimates of mean discounted ICERs per patient undergoing GH treatment for GHD (2000 prices)*

Condition: GHD	Mean incremental total cost per patient	Mean cm gained per patient*	Incremental cost per cm gained (ICER)	Estimate of uncertainty range (minimum to maximum ICER)†
Base case 1	£53,373	8.85 cm	£6,029 per cm	£1,385–11,853 per cm
Base case 2	£43,086	7.55 cm	£5,708 per cm	£1,660–11,209 per cm

* *Adjusted for drop-outs and gender (when data were available) and discounted*
† *One-way sensitivity analysis results (see appendix 10)*

TABLE 11 *Scenario analysis: estimates of mean discounted ICERs in GHD*

Scenario analysis	ICER estimate or range: base case 1	ICER estimate or range: base case 2
Scenario A	£4760–6709	£5708–8046
Scenario B	£5960–6128	£5599–5865
Scenario C	£4918	£4661
Scenario D	£7940	£8459
Maximum *BNF* price for drug therapy	£6756	£6395

the incremental cost of treatment for each centimetre in final height gained with GH treatment over growth monitoring (no GH treatment).

As seen by the wide range in minimum and maximum estimates of uncertainty, the impact of uncertainty surrounding key parameters in the model was clearly important. Full details of one- and two-way sensitivity analyses (for all conditions) are presented in appendix 10. The three most important parameters were the values attached to drug dose, length of treatment and effect size. The minimum and maximum ICER estimates require careful interpretation because the parameter values incorporated were values not necessarily achievable in practice.

For the ICERs in *Table 11*, the scenarios presented reflect realistic treatment possibilities. In addition, the ICER for each centimetre gained in treatment

is shown if GH cost was set at the maximum *BNF* value and if treatment duration was 5–12 years (with the same outcome as the duration of treatment in the base cases). The longer duration of treatment is likely to become more common as diagnoses are made earlier.

The actual cost of GH treatment varies with the average weight of the child. The annual treatment cost for a 30-kg child was £6103 (93.6% drug cost and 6.4% cost of monitoring).

Summary of effectiveness and cost-effectiveness of GH in children with GHD

- The effects of GH in children with GHD are reported from one RCT that tested 49 patients and two non-RCTs reporting final height in 369 and 674 patients.
- The published RCT received a quality score of 2/5. The GHD group (defined as GH peak < 7 µg/l) was not placebo controlled, and children received either high- or low-dose GH. However, the partially GH-deficient group received either low-dose GH or no treatment. This group (defined as GH peak of 7–10 µg/l) could also be considered GH-deficient by some definitions of GHD.
- Results from the published RCT[23] show that GH therapy is effective in promoting growth in GH-deficient children, and improvements can be achieved when assessed using HtSDS and GV measures before and after treatment.
- Two retrospective single-cohort studies evaluated height before and after treatment in children with idiopathic GHD. These studies were uncontrolled and may suffer from sampling bias, but are the best data available on the effect of GH on final height in patients with GHD.
- The final height in children with GHD seems to improve by approximately 1.3–1.6 SD from pretreatment measures. Using current adult height norms and assuming that untreated children would maintain their pretreatment HtSDS at final height, the height gain due to GH treatment would be approximately 8.7–10.7 cm for boys and 7.7–9.5 cm for girls. This estimate of height gain attributable to GH is likely an underestimate because the assumption that children with GHD would have a final HtSDS equivalent to their HtSDS at the inception of treatment is probably not valid (their final HtSDS if left untreated would likely be lower than at treatment inception).
- It is possible that the Cutfield study[44] underestimates the effectiveness of GH in view of current treatment, which starts earlier and uses a higher dose per kilogram and daily injections.
- GHD has several aetiologies, and therefore treatment duration and age at treatment inception will vary.
- No serious adverse effects of GH treatment were reported in the included studies.
- The incremental cost of GH treatment for one child with GHD (for 5–8 years of GH treatment) was estimated to range from £43,100 to £53,400.
- The incremental cost of each centimetre in final height gained due to GH treatment (ICER) was approximately £5700–6030 but could range from £1385 to £11,853.
- The annual cost of GH treatment of a 30-kg child was £6103 (93.6% drug cost and 6.4% cost of monitoring).

Chapter 5

GH in Turner syndrome

Background

TS is the most common sex-chromosome abnormality in females and affects approximately 3% of females conceived.[59] However, because there is a high rate of spontaneous miscarriage, TS affects one in 1500 to 2500 live-born females.[59] Affected individuals either have a single X chromosome (45,X) or display chromosomal mosaicism (45,X/46,XX). Females with TS may present with any of a number of physical abnormalities (e.g. growth failure, gonadal dysgenesis, abnormalities of some internal organs, 'square' appearance) as well as some cognitive difficulties (although overall intelligence is generally normal).[59]

TS is one of the most common organic causes of short stature in girls, and 80–100% of girls with TS will have growth failure.[59] Short stature is the most common finding in TS and is almost always present, even in patients who do not display other clinical features. However, short stature may not be present if the girl has inherited her remaining X chromosome from a tall parent.

TS usually involves mild intrauterine growth retardation (1 SD below normal), decreased growth rates during infancy and childhood (generally about 2 SD below the normal mean) and pronounced lack of pubertal growth, resulting in height approximately 4 SD below the mean at about age 14 years.[59,60] Thereafter, growth continues slowly back toward the norm, with final height about 2.6 SD below the mean of normal adult women.[60] The growth phase is more prolonged than in normal girls, generally not being completed before the end of the second decade of life. Although the mechanism of growth failure in TS is not well understood, it "probably results from an impaired response to growth hormone combined with an underlying skeletal dysplasia".[61]

The adult height of untreated girls with TS generally averages approximately 143–144 cm (56–57 inches); however, studies of final height in TS have reported means ranging from 136 cm to 147 cm.[62] This final height is approximately 20–21 cm (8 inches) shorter than normal women within their respective population. The final height of untreated girls with TS is related to the average of the parents' heights. Although the mean final height of groups of girls with TS generally falls within a fairly narrow range, there is a great deal of variability among individuals.[62]

Use of GH in TS

TS does not involve GHD, and not all girls with TS will need GH treatment. A minority will reach a final height within the normal range without treatment, and a few will be diagnosed too late for effective treatment. However, it has become common practice to treat girls with TS with GH and often with an anabolic steroid (e.g. oxandrolone) as well. A high dose of GH is used because there is thought to be a relative lack of sensitivity to GH in TS. The use of GH in TS is not replacement therapy, and therefore doses are supraphysiological. Whether dose is computed by weight or body surface area can have a significant effect on the dose given and is particularly relevant in older girls with TS who may have problems with excessive weight gain. Among younger girls (age 5 years), a dose based on surface area was as much as 33% greater than one based on weight, whereas among older girls (age 15 years) the dose based on surface area could be as much as 10% less than that based on weight.[63]

The dose of GH generally recommended for use in TS is not often specified, but a dose of 0.375 mg/kg/week has been suggested by the American Association of Clinical Endocrinologists (AACE).[64]

A recent prescription survey in 1998[8] (see *Table 2*) found that approximately 390 girls with TS were being treated with GH in England and Wales.

Oestrogen is administered to promote puberty, but there does not appear to be any evidence that it is a growth-promoting agent. Indeed, the opposite appears to be the case, because oestrogen therapy that was started at younger ages resulted in reduced final heights compared with girls in whom oestrogen was started later (e.g. after age 14 years).[59] However, it should be noted that these studies involved rapid induction of puberty, which is not current UK practice. It is now generally

thought that it is important to administer GH for as long as possible before starting oestrogen therapy.

Quality and quantity of effectiveness studies

There have been many studies of GH in TS, but few RCTs. Therefore, the best level of evidence to evaluate the efficacy of GH in TS is very limited in quantity. Four publications from three RCTs as well as four non-RCTs met the inclusion criteria (*Table 12*).

RCTs

Three RCTs that compared growth on GH therapy with a no-treatment control met the inclusion criteria (*Tables 12* and *13*, with details in appendix 13). One of these trials presented final height data[24] and reported short-term psychological outcomes in a separate publication.[13] Another reported short-term growth outcomes.[25,26] The third trial[27] reported short-term cognitive outcomes in a subset of participants from an RCT continuing to final height, but the growth outcomes have not been reported from this trial.

All the studies included girls with TS. In the Canadian trial, the girls were between 7 and 13 years of age at the start of the study.[13,24] In the other growth trial,[25,26] the girls averaged age 9.3 years. In the Ross trial,[27] participants averaged approximately 9.6 years of age.

The GH dose in the Canadian trial was 0.30 mg/kg/week, administered over six injections per week. The GH dose in the cognitive trial was 0.30 mg/kg/week, in three injections per week. Rosenfeld's study[25,26] was one of the earliest RCTs evaluating GH in TS and used an early formulation of GH, met-hGH (methionyl human GH), in a

TABLE 12 *Summary of study details: TS*

Reference	Control group	Intervention	Participants	Duration
CGHAC, 1998[24] Jadad score: 2/5	Randomised	GH vs no treatment GH: 0.3 mg/kg/week, 6 times weekly	40 (GH) 29 (no treatment) All with TS	Not reported
Rosenfeld, 1990[25] and 1989[26] Jadad score: 2/5	Randomised	GH vs no treatment vs OX vs GH + OX Met-hGH: 0.375 mg/kg/week in 3 injections	17 (GH) 18 (no treatment) All with TS	1-year results reported
Rovet & Holland, 1993[13] (psychological aspects of CGHAC trial) Jadad score: 2/5	Randomised	GH vs no treatment GH: 0.30 mg/kg/week in 6 injections	51 (GH) 44 (no treatment) All with TS	18 months
Ross *et al.*, 1997[27]	Randomised	GH vs placebo GH: 0.30 mg/kg/week in 3 injections	20 (GH) 20 (placebo) All with TS	1–7 years GH group mean: 3.1 years Placebo group mean: 2.5 years
Dacou-Voutetakis *et al.*, 1998[46]	Declined treatment or lack of GH availability	GH vs no treatment Mean GH dose: 0.23 mg/kg/week	35 (GH) 27 (no treatment) All with TS	Average duration: 2.7 years
Hochberg & Zadik, 1999[47]	Declined treatment	GH vs no treatment GH: 8.2 mg/m^2/week	25 (GH) 24 (no treatment) All with TS	Average duration: 5.1 ± 1.9 years
Pasquino *et al.*, 1996[48]	Retrospectively matched for CA, BA and karyotype	GH vs no treatment GH: 0.17 mg/kg/week in year 1, 0.33 mg/kg/week thereafter	18 (GH) 18 (no treatment) All with TS	Average duration: 4.5 ± 0.9 year
Taback *et al.*, 1996[49]	Declined treatment	GH vs no treatment GH: 0.35 mg/kg/week	17 (GH) 14 (no treatment) All with TS	Average duration: 3.6 years

CA, chronological age; BA, bone age; OX, oxandrolone

dose of 0.375 mg/kg/week, administered over three injections per week. The Rosenfeld study also included two additional groups (treated with oxandrolone, and GH plus oxandrolone).

The outcome measures were growth measures in the Canadian trial and the Rosenfeld trial. For the latter trial,[25,26] the primary outcome was GV over 1 year, whereas the former trial[24] reported final height. The psychological study associated with the Canadian trial[13] reported a range of self-report measures of self-concept and psychosocial adjustment as well as parental ratings of behaviour and achievement. The Ross trial[27] reported a wide range of neuropsychological measures of cognitive abilities.

The RCTs all received Jadad quality scores of 2/5. One growth study[24] was available only in abstract form, and therefore methodological detail could not be adequately evaluated. The associated psychological study[13] did not report the method of randomisation and was not double-blind. The baseline comparability of groups was unclear, and there were a large number of drop-outs. The other growth study[25,26] did not describe the method of randomisation and was not double-blind. The third trial considering cognitive outcomes[27] did not describe the method of randomisation, and it was not clear how the subset of participants reported on were drawn from the larger RCT.

Studies reporting final height

Because only limited final height information from one RCT was available, additional evidence on the effect of GH on final height in TS was sought. Four non-randomised studies met the inclusion criteria for final height studies (*Tables 12* and *13*, with details in appendix 14).[46–49]

TABLE 13 *Summary of results assessing the effectiveness of GH in TS*

Reference	Outcome (mean)	GH		Placebo or no treatment		Statistical comparison GH vs control
		After treatment	Δ	After	Δ	
RCTs						
CGHAC, 1998[24]	FH (cm)	146.2	24.6	141.4	17.0	Not reported
	Final HtSDS		+1.5*		+0.3	Not reported
Rosenfeld, 1990[25] and 1989[26]	GV (cm/year)	6.6		3.8		Not reported
	GVSDS	+3.1		–0.1		Not reported
Rovet & Holland, 1993[13]	Psychological self-report	See text and appendix 13				
Ross *et al.*, 1997[27]	Cognitive tests	See text and appendix 13				
Non-RCTs						
Dacou-Voutetakis *et al.*, 1998[46]	FH (cm)	146.1		144.0		NS
Hochberg & Zadik, 1999[47]	FH (cm)	147.3		142.9		
Pasquino *et al.*, 1996[48]	FH (cm)	147.6		142.2		
Taback *et al.*, 1996[49]	FH (cm)	148.0†		140.7†		$p = 0.004$
Dacou-Voutetakis *et al.*, 1998[46]	Final HtSDS	+0.24		+0.07		NS
Pasquino *et al.*, 1996[48]	Final HtSDS	+1.0 (Lyon norm[7])		–0.2 (Lyon norm[7])		$p < 0.05$
		+0.9 (Italian norm)		+0.04 (Italian norm)		$p < 0.05$

Δ, *change from baseline; FH, final height; NS, not statistically significant*

Note: SDS values are relative to norms for untreated TS

* *Within-group before/after comparison was statistically significant*

† *Median*

Dacou-Voutetakis and co-workers[46] administered GH at an average dose of 0.23 ± 0.4 mg/kg/week for an average duration of 2.7 years, beginning at an average age of 12 years. Hochberg and Zadik[47] administered GH at a dose of 8.2 mg/m^2/week for an average duration of 5.1 ± 1.9 years, beginning at an average age of 10.7 years. Pasquino and colleagues[48] administered GH at a dose of 0.17 mg/kg/week in year 1 and 0.33 mg/kg/week subsequently for an average duration of 4.5 years, beginning at an average age of 13 years. Taback and co-workers[49] administered GH at a dose of 0.35 mg/kg/week (maximum of 15 mg/week) for an average duration of 3.6 years, beginning at a median age of 10.2 years. In each of these studies, control participants were untreated.

Because these studies were sought only to provide information about final height, the only outcome considered was final height.

The primary methodological problem with these studies was that two trials[46,49] did not have comparable groups at baseline – the groups differed in age of initiation of oestrogen therapy[46] and in baseline height and predicted height.[49] Other problems were that participants self-selected into treatment versus control groups in three studies,[46,47,49] and there was no information about sampling.

Assessment of effectiveness of GH in TS

Available evidence suggests that GH significantly increases both short-term GV and final height in girls with TS (*Table 13*).

Short-term outcomes

GV

Short-term growth results were available from the Rosenfeld RCT.[25,26] The GV of girls on GH for 1 year was 6.6 ± 1.2 cm/year. The GVSDS was +3.1 ± 1.2. The GV in the untreated control group was 3.8 ± 1.1 cm/year, equating to a GVSDS of –0.1 ± 1.0. When GH was added to oxandrolone, 1-year GV was approximately 2.2 cm greater than when oxandrolone was given alone. No statistical comparisons between groups were reported. It should be noted that this study used 3 injections per week rather than the now usual 6–7 injections. Therefore, effectiveness may have been less than would be seen with the usual dosing regimen.

Psychological and cognitive function

Rovet and Holland[13] assessed self-concept and psychosocial perceptions. From self-reports after 18 months of treatment, it was reported that girls treated with GH had significantly better scores than untreated girls in global self-concept, appearance, intelligence and peer relationships. Treated girls also reported more friendships and popularity and less teasing. Parents of treated girls reported less hyperactivity. However, parents' perception of mathematics performance in treated girls decreased over time. Correlations between GV and other factors showed that a high growth rate was significantly associated with fewer somatic complaints, less hyperactivity, more friends, better social competence, greater popularity, less teasing, improved perceived appearance and improved perceived intelligence. It should be noted that this trial was an open trial and reported subjective outcomes that could be influenced by treatment status. For instance, subjective reports may have been affected by social desirability or justification of effort. However, the correlations between growth and psychological outcomes make these explanations less likely. There was no objective verification of perceived changes. There was also a lack of clarity as to whether differential drop-out and differing characteristics among drop-outs may have affected these results.

The Ross trial[27] reported on a wide range of standardised neuropsychological tests of cognitive function. When using statistical corrections for multiple comparisons, no test revealed a significant difference between girls treated with GH and those on a placebo.

Unfortunately, none of the tests employed in these two trials yield scores that are appropriate to use in economic evaluation.

Final height outcomes

Final height

One RCT has followed girls with TS to their final height. This study, conducted by the Canadian Growth Hormone Advisory Committee,[24] is ongoing. The data presented are from an abstract. The abstract reports results from approximately half of the girls in the original randomisation group. The duration of treatment was not reported and could not be obtained. The girls who were treated with GH achieved a mean final height of 146.2 ± 6.5 cm, and those who were untreated grew to 141.4 ± 4.7 cm. Although there was no information given about co-variates, it was reported that the mean GH effect estimated

by analysis of co-variance (ANCOVA) was 6.5 ± 1.1 cm ($p < 0.001$) for final height.

The results from the four non-randomised studies assessing final height are summarised in the order of size of the trials. Mean final height in the Dacou-Voutetakis study[46] in treated girls was 146.1 ± 6.6 cm and in untreated girls was 144.0 ± 6.1 cm. There was no significant final height advantage in the treated group. In the Hochberg and Zadik study,[47] mean final height in the treated girls was 147.3 ± 4.9 cm and in untreated girls was 142.9 ± 5.1 cm. In the Pasquino study,[48] mean final height was 147.6 ± 7.3 cm in the treated girls and 142.2 ± 4.9 cm in untreated girls. In the Taback study,[49] median final height was 148.0 cm in the treated girls and 140.7 cm in the untreated girls ($p = 0.004$); however, it should be noted that the girls in the treated group were taller and had a greater projected height (4.2 cm greater) than the control group at the initiation of the trial.

HtSDS

In the Canadian study,[24] the change in the HtSDS (based on a TS standard) from the start of the trial was +1.5 ± 0.5 in the GH group and +0.3 ± 0.4 in the untreated control group.

The heights in the Dacou-Voutetakis study[46] equated to +0.24 ± 1.0 HtSDS for the treated girls and +0.07 ± 0.9 HtSDS for the untreated girls (based on a TS standard). This was a non-significant difference. Based on the Lyon TS standard,[7] the heights in the Pasquino study[48] equated to an HtSDS of +1.0 ± 1.6 in treated girls and –0.2 ± 1.1 in the untreated girls ($p < 0.05$).

Adverse effects

There was no discussion of adverse effects in the RCTs nor was there mention of adverse effects in the Dacou-Voutetakis study.[46] Among the remaining non-randomised studies, it was noted that there were no major side-effects or relevant metabolic changes. It was noted in one study that "hyperinsulinaemia with normal glucose tolerance was observed in most patients in whom it was looked at".[47]

Cost-effectiveness of GH in TS

Model parameters and data

A model of the cost-effectiveness of GH treatment in TS was populated with the best available evidence. *Table 3* in chapter 2 lists the model parameters that were common to all five conditions. The additional parameters that were specific to TS are shown in *Table 14*. The effect of GH on final height in children with TS was taken from the effectiveness review above.

The estimates of the cost and cost-effectiveness of using GH in TS were modelled using the parameters above in the context of three scenarios (see *Table 15*). The scenarios describe important factors that influence successful treatment and the cost of treatment.

Costs, effects and ICERs

The costs of GH treatment and growth monitoring are based upon costs associated with the appropriate event pathway (see appendix 9). The event pathway for no GH treatment is depicted in diagram A of appendix 9. The event pathway for

TABLE 14 *Model parameters, values and data sources for GH in TS*

Parameter	Value and source
Population data	
Sex distribution of patients	100% females
Effectiveness data	
Base case 1:	
Length of GH treatment (assumes child aged 11 years)	5 years[24]
Final height gain – benefit uniformly spread over treatment period	4.8 cm[24]
Base case 2:	
Length of GH treatment (assumes child aged 11 years)	5 years[47]
Final height gain – benefit uniformly spread over treatment period	4.4 cm[47]
Investigation and treatment parameters	
Drug dose – based on average age- and sex-related weight at 50th percentile and not adjusted during puberty	0.30 mg/kg/week[24] (0.17–0.70 mg/kg/week[61])
GH treatment drop-out rate after first year of treatment	17%[24]
Drop-out rate from monitoring after first year of monitoring	41%[24]

TABLE 15 *Scenarios for base cases 1 and 2: GH treatment in TS*

Scenario	Description
Scenario A	Same parameter values as either base case, with the exception of the assumption about length of treatment, which is assumed to vary between 8 and 12 years
Scenario B	Same parameter values as either base case, with the exception of the assumption about drop-out rate, which is assumed to vary between 0% and 20%
Scenario C	Same parameter values as either base case, with the exception of the administration of drug dose, which is based on age- and sex-related weight at the 9th to 25th percentiles

TABLE 16 *Estimates of mean discounted recurrent costs per patient with TS undergoing GH treatment and growth monitoring (2000 prices)*

Condition: TS	Mean total cost of GH treatment	Mean drug cost (% of total cost)	Mean cost of growth monitoring
Base cases 1 and 2	£62,621	£60,646 (97%)	£852

TABLE 17 *Estimates of mean discounted ICERs per patient undergoing GH treatment for TS (2000 prices)*

Condition: TS	Mean incremental total cost per patient	Mean cm gained per patient*	Incremental cost per cm gained (ICER)	Estimate of uncertainty range (minimum to maximum ICER)†
Base case 1	£61,770	3.87 cm	£15,997 per cm	£4,690–36,855 per cm
Base case 2	£61,770	3.54 cm	£17,429 per cm	£5,116–40,205 per cm

* *Adjusted for drop-outs and discounted*
† *One-way sensitivity analysis results (see appendix 10)*

TABLE 18 *Scenario analysis: estimates of mean discounted ICERs for TS*

Scenario analysis	ICER estimate or range: base case 1	ICER estimate or range: base case 2
Scenario A (length of treatment, 8–12 years)	£20,194–22,260 per cm	£22,029–24,284 per cm
Scenario B (0–20% drop-outs)	£15,360–16,113 per cm	£16,756–17,577 per cm
Scenario C (9th to 25th percentile weight for age and sex)	£13,014–14,382 per cm	£14,197–15,689 per cm
Maximum *BNF* price for drug therapy	£17,935 per cm	£19,566 per cm

the decision as to whether to offer GH treatment and whether treatment will be accepted in TS is depicted in diagram D. Diagram F depicts the event pathway for GH treatment in TS. These event pathways specify the various parameters that must be included in order to realistically estimate the costs associated with GH treatment and no treatment (i.e. growth monitoring) in TS.

Costs were estimated using the appropriate parameters specified from the event pathways and the treatment assumptions outlined in the scenarios above. *Table 16* reports estimates of mean discounted recurrent costs achieved under the two base cases.

Table 17 reports the ICERs under both base cases, reflecting the incremental cost of treatment for each centimetre in final height gained with GH treatment over growth monitoring (no GH treatment).

In *Table 18,* ICER scenarios are presented that reflect realistic treatment possibilities.

The annual cost of GH treatment varies with the weight of the child. The annual cost for GH treatment of a 30-kg child was £10,126 (96.8% GH cost and 3.2% monitoring cost).

Summary of effectiveness and cost-effectiveness of GH in children with TS

- Three RCTs met inclusion criteria, with one of these RCTs reporting growth and psychological outcomes in separate publications. Two growth trials included 69 and 35 participants. Two psychological reports included 48 and 40 participants.
- The RCTs lacked information about randomisation, and only one was double-blind.
- The available evidence suggests that GH is effective in TS in increasing short-term GV by perhaps approximately 2.8 cm/year over 1 year.[25,26] This result may be an underestimate of the effects that would be expected with dosing 6–7 times per week, rather than 3 times per week.
- Girls treated with GH were approximately 5 cm taller (4.8 cm) than untreated girls in the one RCT that has reported final height from a subset of the original sample.[24]
- Four non-randomised studies that included treatment and no-treatment groups reported final height in TS. These studies lacked appropriate sampling, and there were problems with equivalence of comparison groups. The sample sizes ranged from 123 participants[46] to 31 participants.[49]
- In the non-RCTs, the girls treated with GH were approximately 4–5 cm taller at final height than untreated girls. One study reported no statistically significant improvement in final height in the GH-treated group (mean final height was 2.1 cm more than in the untreated group),[46] and another reported a final height gain of approximately 7 cm (based on medians; it is also noteworthy that the treated girls were taller at baseline in this study).[49] There is considerable individual variability in response to GH treatment.
- In one trial, treated girls reported higher scores on measures of self-concept and psychosocial functioning than untreated girls.[13] In another trial, GH treatment did not produce any significant changes in cognitive performance.[27]
- All studies included little or no discussion of adverse effects. None mentioned major adverse effects or significant metabolic changes.
- It is possible that the final height results underestimate the effects of GH. Despite current recommendations that treatment start early (ideally before age 8 years), all the reported studies started treatment in older children (approximately 10–13 years of age, if reported). Therefore, it remains possible that studies beginning GH treatment at an earlier age and continuing until final height is attained would result in greater height gains than reported here.
- The incremental cost of GH treatment (for 5 years) for one child with TS was estimated to be approximately £61,800.
- The incremental cost of each centimetre in final height gained due to GH treatment (ICER) after 5 years of treatment was between £16,000 and £17,400, but could range from £4690 to £40,205.
- The annual cost of GH treatment for a 30-kg child was £10,126 (96.8% GH cost and 3.2% monitoring cost).

Chapter 6

GH in chronic renal failure

Background

CRF is defined as a persistent elevation of serum creatinine and/or a persistent elevation of serum urea level. Terminal renal failure is when the disease results in a need for dialysis, renal transplantation or death.[65] There are a large number of aetiologies that can lead to CRF or terminal renal failure, including congenital disorders, glomerular disorders and infectious origins.

Because many cases of CRF progress to the point of transplantation, the use of GH can be considered both in patients undergoing dialysis (either haemodialysis or peritoneal dialysis) or post-transplantation. Growth failure is associated with CRF and may be due to several factors, including acidosis, rickets, GH resistance, inadequate nutrition and anorexia.[66] After transplantation, other factors such as chronic graft rejection and steroid treatment may interfere with growth and development.[4]

Growth and final height are generally reduced in cases of CRF. However, given the wide range of aetiologies, some children have had considerable growth before CRF and may achieve normal or near-normal height, whereas others have growth failure from early childhood. Growth impairment can begin when glomerular filtration rate is less than 50% of normal and is universal when this rate falls below 25% of normal.[67] Approximately 60% of patients with CRF have congenital disorders, and growth failure is a significant problem in this population.[4] These children are generally of normal length at birth, but drop below the 3rd percentile for height within the first year and remain generally parallel to the normal percentiles through childhood (to age 10 years).[4] Mean height collected retrospectively for a congenital CRF population from birth to age 10 years was –2.37 SD ± 1.6.[4] Final height is reduced below the 3rd percentile in one-third of all patients who enter end-stage renal failure in childhood.[4]

Use of GH in renal disease

Although the mechanism of growth failure in children with CRF is not well described and almost certainly involves a number of factors, it is the case that a substantial proportion of such children fail to achieve their target heights. For this reason, GH has been used to try to increase growth and final height in such patients. GH has been used in children with CRF before transplantation as well as after receiving renal allografts.

Surveys by the UK Renal Registry suggest that approximately 530 patients under age 15 years were in the registry in 1998 across the UK and Ireland.[68] How many of these patients would be of short stature and would opt for GH treatment is difficult to determine, although a prescription survey in 1998 suggested that very few of these patients (approximately 55) were receiving GH.[8] The Renal Registry is now collecting data on GH use and growth in these children.

The usual dose of GH in CRF has been 0.3–0.35 mg/kg/week, given in 6–7 injections. It has been noted that patterns of prescribing GH in children with renal disease have been changing, such that more children are being treated with GH prior to renal transplant rather than after. This decreases any risk of GH treatment affecting transplant rejection.[51] Most clinicians consider that GH treatment in children with CRF is an attempt to maintain age-appropriate growth so that, with the re-establishment of normal GH responsiveness post-transplant, the patients come closer to achieving their target height.[69]

Quality and quantity of effectiveness studies

Five RCTs and two non-RCTs met the inclusion criteria (*Table 19*).

RCTs

Five RCTs met the inclusion criteria (*Tables 19* and *20*, with details in appendix 15). Three trials[28–30] included patients who were in CRF but who had not received a renal allograft. The doses of GH used were 0.35 mg/kg/week in two trials[28,29] and 9.3 mg/m^2/week in the third.[30] The average ages of the children at the start of each trial were approximately 9 years,[30] 6 years[28] and 6 years.[29]

TABLE 19 *Summary of study details: renal disease*

Reference	Control group	Intervention	Participants	Duration
Fine *et al.*, 1994[28] Jadad score: 2/5	Randomised	GH vs placebo GH: 0.35 mg/kg/week	82 (GH) 43 (placebo) All with CRF	2 years
Powell *et al.*, 1997[29] Jadad score: 2/5	Randomised	GH vs no treatment GH: 0.35 mg/kg/week	30 (GH) 14 (no treatment) All with CRF	1 year
Hokken-Koelega *et al.*, 1991[30] Jadad score: 3/5	Randomised Crossover Group A: GH then placebo Group B: placebo then GH	GH vs placebo GH: 9.3/m^2/week	16 All prepubertal children with CRF	6 months in GH and placebo groups
Broyer, 1996[31] Jadad score: 2/5	Randomised	GH vs no treatment GH: 0.33 mg/kg/week	106 (GH) 97 (no treatment) All post-transplant	2 years (year 1 results presented)
Hokken-Koelega *et al.*, 1996[32] Jadad score: 4/5	Randomised Crossover Group A: GH then placebo Group B: placebo then GH	GH or placebo GH: 9.3 mg/m^2/week	11 All prepubertal and post-transplant	6 months in GH and placebo groups
Haffner *et al.*, 2000[50]	Little or no growth retardation at baseline, declined treatment or ineligible due to advanced puberty	GH: 0.33 mg/kg/week	38 (GH) 50 (no treatment) Mixed CRF and post-transplant	Median duration: 5.3 years
Janssen *et al.*, 1997[51]	Historical	GH: 0.33 mg/kg/week	17 (GH) 14 (no treatment) All post-transplant	Median duration: 3.4 years

Two RCTs were conducted in patients who were all post-transplant.[31,32] The GH doses used were 0.33 mg/kg/week[31] and 9.3 mg/m^2/week.[32] The Broyer trial[31] included both treated and untreated groups for 1 year. The crossover trial[32] placed the same children on GH or placebo for 6 months each. The average age of the children at the start of both trials was approximately 12 years.

The RCTs all considered relatively short-term outcomes, including HtSDS (or change in HtSDS) and GV (or change in GV). Two of the trials were crossover trials, with 6 months on GH and placebo.[30,32] Two trials[29,31] included both patients on treatment and controls for 1 year, and one followed the treatment and control groups for 2 years.[28]

Three trials[28,29,31] received Jadad quality scores of 2/5, and two trials[30,32] received Jadad scores of 4/5. In none of the trials were the methods of randomisation described, and trials with no-treatment controls were not double-blind. Two trials[30,32] were double-blind and used a placebo control. However, these two crossover trials[30,32] did not include a wash-out period between the GH and placebo phases (and vice versa).

Studies reporting final height

Two non-randomised studies were included because no final height data were available in the context of an RCT (*Tables 19* and *20*, with details in appendix 16). The outcomes of interest for these studies were final height and final HtSDS. (A mention has been found of final height data from a group of 18 treated renal allograft recipients; however, the cited reference could not be located and the author could not be contacted.)

Haffner and co-workers[50] included children who were either pre- or post-transplant. The GH dose was 0.33 mg/kg/week for a median duration of 5.3 years, starting at approximately age 10 years.

TABLE 20 *Summary of results assessing the effectiveness of GH in renal disease*

Reference	Outcome (mean)	GH		Placebo or no treatment		Statistical comparison GH vs control
		After treatment	Δ	After	Δ	
RCTs						
Fine *et al.*, 1994[28]	HtSDS	–1.6	+1.3*	–2.9	–0.1	
Powell *et al.*, 1997[29]	HtSDS		+0.8		0.0	$p < 0.0001$
Broyer, 1996[31]	HtSDS					
	Prepubertal		+0.6			$p < 0.0001$
	Entering puberty		+0.6			$p < 0.0001$
	Pubertal		+0.7			$p < 0.0001$
Fine *et al.*, 1994[28]	GV (cm/year)					
	Year 1	10.7		6.5		$p < 0.00005$
	Year 2	7.8		5.5		$p < 0.00005$
Powell *et al.*, 1997[29]	GV (cm/year)	9.1		5.5		$p < 0.0001$
Hokken-Koelega *et al.*, 1991 (CRF)[30]	GV (cm/6 months)	Group A: 5.2 Group B: 4.4	*	Group A: 1.5 Group B: 2.4	*	$p < 0.001$
Hokken-Koelega *et al.*, 1996 (post-transplant)[32]	GV (cm/6 months)	Group A: 5.3 Group B: 3.9	*	Group A: 1.5 Group B: 1.9		
Hokken-Koelega *et al.*, 1991 (CRF)[30]	GVSDS	Group A: 6.9 Group B: 5.0		Group A: –3.0 Group B: –0.5		$p < 0.001$
Broyer, 1996[31]	GVSDS					
	Prepubertal	3.7		0.3		$p < 0.0001$
	Entering puberty	4.9		0.6		$p < 0.0001$
	Pubertal	4.3		0.7		$p < 0.0001$
Hokken-Koelega *et al.*, 1996 (post-transplant)[32]	GVSDS	Group A: 9.1 Group B: 5.3		Group A: –1.3 Group B: –0.4		$p < 0.0001$
Non-RCTs						
Haffner *et al.*, 2000[50]	FH (cm)	Boys: 165.2 Girls: 156.2		Boys: 162.1 Girls: 151.9		$p = 0.021$ $p = 0.028$
Janssen *et al.*, 1997[51]	FH (cm)	Boys: 162.7 Girls: 151.0		Boys: 153.5 Girls: 143.0		$p < 0.01$ NS
Haffner *et al.*, 2000[50]	Final HtSDS	–1.6		–2.1	–0.6*	
Janssen *et al.*, 1997[51]	Final HtSDS	–1.8 –1.9		–3.2 –3.2		$p < 0.01$ NS

Δ, *change from baseline*

* *Within-group before/after comparison was statistically significant. Change scores (or baselines) were not reported, but after-treatment values were reported to be significantly different from baseline values*

In the study by Janssen and colleagues,[51] children treated with GH post-transplant were retrospectively compared with a historical control group. The GH dose was 0.33 mg/kg/week for a median duration of 3.4 years, starting at approximately age 14 years.

In one study,[50] patients self-selected into treatment or no treatment, resulting in a control group that was taller than the treatment group at baseline. This could lead to an underestimation of the treatment effect. In the other study,[51] the treatment group was evaluated retrospectively and compared with historical controls, which could result in biased subject selection.

Assessment of effectiveness of GH in renal disease

Available results suggest that GH treatment in CRF increases both short-term growth and final height (*Table 20*).

Short-term outcomes: CRF

HtSDS

Fine and co-workers[28] and Powell and colleagues[29] reported a significantly greater improvement in HtSDS in treated than in untreated children with CRF. In one trial, this improvement averaged 1.3 SDS over 2 years ($p < 0.00005$, based on a before vs after within-group comparison),[28] whereas in the other trial, there was an average increase in HtSDS of 0.8 ± 0.5 SDS in 1 year ($p < 0.0001$).[29] There was no significant change in the HtSDS of the untreated groups in these trials.

GV

GV was also significantly improved in treated versus control groups. In the Fine trial,[28] GV was greater in the treated group than in the placebo controls, in both the first and second years of the trial ($p < 0.00005$ for both), despite lower GV in the second year than in the first. In the Powell trial,[29] GV averaged 3.6 cm greater in the treated children than in the untreated children with CRF ($p < 0.0001$). In the Hokken-Koelega crossover trial,[30] the mean GH-induced increase in GV compared with placebo was 2.9 cm per 6 months (95% confidence interval [CI], 2.3 to 3.5 cm). This increase in GV was also significant when converted to GVSDS.

Short-term outcomes: post-transplant

HtSDS

Broyer[31] reported significantly greater changes in HtSDS over 1 year in treated children than in untreated children post-transplant. This was true in prepubertal children (0.6 ± 0.3 vs 0.1 ± 0.3), children entering puberty (0.6 ± 0.6 vs –0.1 ± 0.4) and pubertal children (0.7 ± 0.5 vs 0.1 ± 0.5) ($p < 0.0001$ for each).

GV

In the Broyer trial,[31] GV was also significantly improved for treated compared with untreated children ($p < 0.0001$; see *Table 20* and appendix 15 for values). In the Hokken-Koelega crossover trial,[32] the mean GH-induced GV compared with placebo was 2.9 cm per 6 months (95% CI, 1.9 to 3.9 cm). When these changes were considered as GVSDS, there were also significant differences between children when they were being treated versus when they were untreated ($p < 0.0001$).

Final height outcomes

Final height

In the Haffner study,[50] the final height of treated boys was 165.2 ± 8.2 cm and that of untreated boys was 162.1 ± 9.0 cm ($p = 0.021$). The final height of treated girls was 156.2 ± 9.8 cm and that of untreated girls was 151.9 ± 6.7 cm ($p = 0.028$). In the Janssen study,[51] the median height of treated boys was 162.7 cm and that of untreated boys was 153.3 cm ($p = 0.01$). The median height of treated girls was 151.0 cm and that of untreated girls was 143.0 cm (not significant).

Final HtSDS

In the Haffner study,[50] the final HtSDS was –1.6 ± 1.2 in the treated children and –2.1 ± 1.2 in the untreated children. These HtSDSs were significantly greater in treated than untreated children (boys, –1.7 ± 1.2 vs –2.1 ± 1.3, respectively, $p = 0.013$; girls, –1.3 ± 1.6 vs –2.1 ± 1.2, $p = 0.02$). In the Janssen study,[51] the HtSDS values were –1.8 in treated males and –3.2 in untreated males ($p = 0.01$). The HtSDS values in females were –1.9 for treated and –3.2 for untreated (not significant).

The Haffner study[50] may give a poor estimate (likely an underestimate) of the treatment effect because the untreated children were taller at the start of the study. The Janssen study[51] began treatment in children relatively late – averaging 14 years of age. This study, with a median duration of treatment of 3.4 years, may underestimate final height effects, but bone age was considerably delayed in these participants relative to their chronological age. However, the use of a historical control group may lead to an overestimation of the treatment effect.

Adverse effects

Within the RCTs, there were very few reported adverse effects. There was one withdrawal due to an allergic reaction to injections.[29] In the two trials that included children post-transplant, allograft rejection was a concern. The crossover study[32] reported no acute rejections and no serious adverse effects. In the longer study,[31] there were 22 rejection episodes in 16 patients in year 1 among those treated with GH. There were nine rejection episodes in seven patients in the control group. The number of patients with acute rejection episodes was higher in the treatment group than in the control group among those patients with a history of more than one prior rejection episode (11 vs 3 patients).

Among the studies following children for a longer term until final height, there was no mention of adverse effects in the Haffner study.[50] Adverse effects in the Janssen study[51] were bone deformities in two patients, clinical facial dysmorphias in

three patients and lipolysis in one patient. However, there was no indication as to whether these effects were attributed to GH. During treatment, there were five chronic rejections, with two transplant glomerulopathies and four acute rejections in the presence of a chronic rejection.

Cost-effectiveness of GH in CRF

Model parameters and data

A model of the cost-effectiveness of GH treatment in CRF was populated with the best available evidence. *Table 3* in chapter 2 lists the model parameters that were common to all five conditions. The additional parameters that were specific to CRF are shown in *Table 21*. The effect of GH on final height in children with CRF was taken from the *Final height outcomes* section on page 32.

The estimates of the costs and cost-effectiveness of using GH in CRF were modelled using the parameters above in the context of three treatment scenarios (see *Table 22*). The scenarios describe important factors that influence successful treatment and the cost of treatment.

Costs, effects and ICERs

The costs of GH treatment and growth monitoring are based upon costs associated with the appropriate event pathway (see appendix 9). The event pathway for no GH treatment is depicted in diagram A of appendix 9. The event pathway for the decision as to whether to offer GH treatment and whether treatment will be accepted in CRF is depicted in diagram D. Diagram F depicts the event pathway for GH treatment in CRF. These event pathways specify the various parameters that must be included in order to realistically estimate the costs associated with GH treatment and no treatment (i.e. growth monitoring) in CRF.

Costs were estimated using the appropriate parameters specified from the event pathways and the treatment assumptions outlined in the scenarios above. *Table 23* reports estimates of mean discounted recurrent costs achieved under the base cases.

TABLE 21 *Model parameters, values and data sources for GH in CRF*

Parameter	Value and source
Population data	
Sex distribution of patients	68% males[8]
Effectiveness data	
Base case 1:	
Length of treatment (assumes child aged 14 years)	3 years[51]
Final height gain – benefit uniformly spread over treatment period	8.82 cm[51]
Base case 2:	
Length of treatment (assumes child aged 11 years)	5 years[50]
Final height gain – benefit uniformly spread over treatment period	3.48 cm[50]
Investigation and treatment parameters	
Drug doses for condition – based on age- and sex-related weight at 50th percentile and not adjusted during puberty	0.33 mg/kg/week[50,51]
Accept treatment	80% (expert opinion)
GH treatment drop-out rate after first year of treatment	16%[28]
Drop-out rate from monitoring after first year of monitoring	28%[28]

TABLE 22 *Scenarios for base cases 1 and 2: GH treatment in CRF*

Scenario	Description
Scenario A	Same parameter values as either base case, with the exception of the assumption about length of treatment, which is assumed to vary between 8 and 12 years
Scenario B	Same parameter values as either base case, with the exception of the assumption about drop-out rate, which is assumed to vary between 0% and 20%
Scenario C	Same parameter values as either base case, with the exception of the administration of drug dose, which is based on age- and sex-related weight at 9th percentile

TABLE 23 *Estimates of mean discounted recurrent costs per patient with CRF undergoing GH treatment and growth monitoring (2000 prices)*

Condition: CRF	Mean total cost of GH treatment	Mean drug cost (% of total cost)	Mean cost of growth monitoring
Base case 1	£54,617	£53,207 (97%)	£611
Base case 2	£69,390	£67,411 (97%)	£965

TABLE 24 *Estimates of mean discounted ICERs per patient undergoing GH treatment for CRF (2000 prices)*

Condition: CRF	Mean incremental total cost per patient	Mean cm gained per patient*	Incremental cost per cm gained (ICER)	Estimate of uncertainty range (minimum to maximum ICER)†
Base case 1	£54,006	7.29 cm	£7,403 per cm	£2,468–15,530 per cm
Base case 2	£68,425	2.84 cm	£24,093 per cm	£7,455–50,538 per cm

* *Adjusted for drop-outs and gender (if data were available) and discounted*
† *One-way sensitivity analysis results (see appendix 10)*

TABLE 25 *Scenario analysis: estimates of mean discounted ICERs in CRF*

Scenario analysis	ICER estimate or range: base case 1	ICER estimate or range: base case 2
Scenario A	£13,170–14,600 per cm	£30,322–33,491 per cm
Scenario B	£6,958–7,543 per cm	£23,267–24,351 per cm
Scenario C	£6,049 per cm	£19,444 per cm
Maximum *BNF* price for drug therapy	£8,314 per cm	£27,057 per cm

Table 24 reports the ICERs under both base cases. These reflect the incremental cost of treatment for each centimetre in final height gained with GH treatment over growth monitoring (i.e. no GH treatment).

In *Table 25*, ICERs are presented for scenarios that represent realistic treatment possibilities.

The annual cost of GH treatment varies with the average weight of the child. The annual treatment cost of a 30-kg child was £11,132 (97.1% GH cost and 2.9% monitoring cost).

Summary of effectiveness and cost-effectiveness of GH in children with renal disease

- Five RCTs met inclusion criteria. Three trials included 125,[28] 44[29] and 16[30] participants with CRF. Two RCTs included 203[31] and 11[32] participants post-transplant.
- The RCTs were of variable quality, but none specified the method of randomisation and only two were double-blind.
- The available evidence suggests that GH is effective in renal patients in increasing short-term height changes by approximately 0.5–0.8 SDS over 1 year[29,31] and 1.3 SDS over 2 years.[28] GV improved by approximately 3–4 cm/year in year 1 and approximately 2.3 cm in the second year of a 2-year study.[28] In the shortest studies, GV was greater in patients on GH than on placebo by approximately 2–4 cm per 6 months.[30,32] Results were similar for patients who were pre- and post-transplant.
- Two non-randomised studies that included treatment and no-treatment groups (one prospective and one retrospective) reported final height in children with CRF/post-transplant. In one of these studies,[50] the groups were not equivalent at baseline. In the other study,[51] there are concerns about sampling because it was retrospective. The sample sizes were 88 patients[50] and 31 patients.[51]

- In these non-RCTs, boys treated with GH were only approximately 3 cm taller than untreated boys in one study,[50] but were approximately 9 cm taller than untreated boys in the other study.[51] Girls treated with GH were approximately 4 cm taller than untreated girls in one study,[50] and 8 cm taller than untreated girls in the other study.[51] The study with the greater final height gains reported medians, was smaller and used historical controls. However, the treatment and control groups in the other study were self-selected, and the control participants were taller at baseline, so treatment effects were likely underestimated.
- Few adverse effects were reported. There is some suggestion that GH treatment may increase the risk of acute rejection episodes in children treated post-transplant, especially among those who have had more than one prior rejection episode.
- The incremental cost of GH treatment for one child with CRF was estimated to be between £54,000 and £68,400.
- The incremental cost of each centimetre in final height gained due to GH treatment (ICER) was between £7400 and £24,100, but could range from £2468 to £50,538.
- The annual cost of GH treatment of a 30-kg child was £11,132 (97.1% GH cost and 2.9% monitoring cost).

Chapter 7

GH in Prader–Willi syndrome

Background

PWS is a genetic disorder that affects approximately 1 in 15,000–25,000 live births. Most patients with PWS have deletion of portions of the paternal 15th chromosome. The syndrome is characterised by hyperphagia, hypogonadism, short final stature, dysmorphic features, hypoventilation and behavioural problems.[70] Generally, unless caloric intake is strictly regulated, children with PWS have a high risk of severe obesity.

Children with PWS have a body composition very similar to that of children with GHD. There is reduced lean body mass and increased fat mass. It has been suggested that PWS involves GHD. Reduced GH secretion is often found in children with PWS. However, because GH secretion is also often suppressed in obese individuals without GHD, it is difficult to determine definitively whether PWS involves a deficiency of GH.[33,35]

Short stature is one of the characteristic symptoms of PWS. In mid-childhood, the height of 50% of these patients is below the 3rd percentile, and final height is below the 3rd percentile in most patients. Mean adult height is approximately 154 cm for men and 145–149 cm for women.[5] Although the cause of short stature in PWS is still uncertain, it is thought that it may be due in part to abnormalities of the GH axis.[5]

Use of GH in PWS

Because of the similarities between PWS and GHD and the findings of abnormalities in the response of the GH axis, treatment with GH has been administered to patients with PWS in hopes of increasing final height as well as having a positive impact on body composition.

Perhaps because GH has only recently been licensed for use in PWS, estimates of the number of children with PWS being treated with GH are not available. Likewise, a recommended GH dose has not been included in professional guidelines. The doses used in the studies included in this review were 0.23, 0.20–0.25 and 0.35 mg/kg/week.

Quality and quantity of effectiveness studies

Three RCTs and one non-RCT met the inclusion criteria (*Table 26*).

RCTs

Three RCTs met the inclusion criteria (*Tables 26* and *27*, with details in appendix 17).[5,33,34] One of these trials[33] included an associated assessment of behaviour reported in a separate publication.[36] The four publications are shown in *Table 26*.

TABLE 26 *Summary of study details: PWS*

Reference	Control group	Intervention	Participants	Duration
Carrel *et al.*, 1999[33] Jadad score: 2/5	Randomised	GH vs no treatment GH: 7 mg/m^2/week	35 (GH) 19 (no treatment) All with PWS	1 year
Lindgren *et al.*, 1997[34] and 1998[35] Jadad score: 2/5	Randomised	GH vs no treatment GH: 0.23 mg/kg/week	15 (GH) 12 (no treatment) All prepubertal with PWS	3 years (only 1 year reported)
Hauffa, 1997[5] Jadad score: 2/5	Randomised	GH vs no treatment GH: 0.35 mg/kg/week (maximum, 2.67 mg/day)	7 (GH) 9 (no treatment) All prepubertal with PWS	1 year
Whitman *et al.*, 2000[36] Jadad score: 2/5	Randomised	GH vs no treatment GH: 7 mg/m^2/week	35 (GH) 19 (no treatment) All with PWS	1 year
Angulo *et al.*, 2000[52]	None	GH: 0.2–0.25 mg/kg/week	16 (GH) All with PWS	4–10 years

TABLE 27 *Summary of study results assessing the effectiveness of GH in PWS*

Reference	Outcome (mean)	GH		Placebo or no treatment		Statistical comparison GH vs control
		After treatment	Δ	After	Δ	
RCTs						
Carrel *et al.*, 1999[33†]	HtSDS	–0.6		–1.6		$p < 0.01$
Lindgren *et al.*, 1997[34] and 1998[35]	HtSDS	–0.4*		–1.8		
Hauffa, 1997[5]	HtSDS		+1.07		–0.25	
Carrel *et al.*, 1999[33]	GV (cm/year)	10.0		5.0		$p < 0.01$
	GVSDS	4.6		–0.7		$p < 0.01$
Lindgren *et al.*, 1997[34] and 1998[35]	GVSDS	6.0*		–1.4		
Hauffa, 1997[5]	GVSDS	5.5		–2.3		$p = 0.0012$
Carrel *et al.*, 1999[33]	% Body fat	38.4		45.8		$p < 0.01$
Lindgren *et al.*, 1997[34] and 1998[35]	% Body fat	30.9*		38.2		
Carrel *et al.*, 1999[33]	Lean body mass (kg)	25.6		21.7		$p < 0.01$
Lindgren *et al.*, 1997[34] and 1998[35]	Fat-free mass (kg)	19.8*		15.2		
Carrel *et al.*, 1999[33]	BMI (kg/m^2)	23.7		25.2		NS
Lindgren *et al.*, 1997[34] and 1998[35]	BMI SDS	2.0*		2.5		
Whitman *et al.*, 2000[36]	Behavioural	See text and appendix 17				All NS
Non-RCT						
Angulo *et al.*, 2000[52]	FH (cm)	Boys: 170 ± 10 Girls: 159 ± 4				
	Final HtSDS	–0.2 ± 1.3				

Δ, *change from baseline*

* *Within-group before/after comparison was statistically significant*

† *The statistical probability values from this trial should be interpreted with caution. The report indicates that the* p*-values are associated with* ***either*** *comparisons between treated and untreated groups* ***or*** *comparisons between baseline and 12 months on treatment within the treatment group*

The outcomes evaluated were all short term. Primary outcomes were growth and body composition outcomes. Those outcomes reported here were judged to be noticeable and relevant to the patients themselves: HtSDS, GV, percentage body fat, lean body mass (or fat-free mass) and BMI. In addition, one trial reported behavioural outcomes.[36]

All three trials were given Jadad quality scores of 2/5. The primary methodological shortcomings were a lack of information about randomisation and sample selection, and a lack of double-blinding. All the trials tested children with a diagnosis of PWS. The GH doses were 7 mg/m^2/week,[33,36] 0.23 mg/kg/week[34,35] and 0.35 mg/kg/week.[5] In all the trials, the control group was untreated. Each of these trials lasted 1 year. The ages of the children at the start of the trials were approximately 6–7 years in one trial,[34,35] 7–8 years in one trial[5] and 10 years in the third trial.[33]

Studies reporting final height

No studies that included both a treated and an untreated group, and that assessed final height

were found. One abstract[52] reported final height in a single group of 16 treated patients (*Tables 26* and *27*, with details in appendix 18). The GH dose was 0.2–0.25 mg/kg/week, and the duration of treatment was 4–10 years. The children averaged age 8.4 years at the start of the study. Little information was available about the study, but there was no control group, and it is unclear how representative the patients were of children with PWS.

Assessment of effectiveness of GH in PWS

The limited evidence available suggests that GH does improve short-term growth and final height in PWS as well as improving body composition (*Table 27*).

Short-term outcomes

HtSDS

After 1 year of treatment, children with PWS who were on GH were approximately one SD taller than untreated children. The Carrel trial[33] reported HtSDSs of –0.6 ± 1.2 versus –1.6 ± 1.2, for treated and untreated children, respectively ($p < 0.01$*). The Lindgren trial[34,35] reported HtSDS of –0.4 versus –1.8 for treated and untreated children, respectively, but the reported significant height improvement was based on a comparison of pretreatment and treatment values within the treated group, rather than a between-group comparison. The Hauffa trial[5] reported a change in HtSDS of +1.07 versus –0.25 for treated and untreated children, respectively (no statistical comparison reported).

GV

In all three trials, the GVSDS of children on GH was significantly improved on GH: 4.6 ± 2.9 versus –0.7 ± 1.9 for treated versus untreated children, respectively ($p < 0.01$*);[33] 6.0 versus –1.4 for comparison with baseline within the treated group ($p < 0.05$);[34,35] and 5.5 versus –2.3 for treated versus untreated children, respectively ($p = 0.0012$).[5]

Body composition

Body composition was improved in children with PWS who were treated with GH. BMI was not significantly affected in the Carrel trial,[33] but it was significantly reduced ($p < 0.05$) relative to baseline in patients in the Lindgren trial.[34,35] Lean body mass was significantly greater in treated than untreated children in one study: 25.6 ± 4.3 kg versus 21.7 ± 5.0 kg ($p < 0.01$).†[33] In another study, fat-free mass was significantly increased relative to baseline within the treated patients ($p < 0.001$).[34,35] Per cent body fat was approximately 7–8% less in treated versus untreated children: 38.4% ± 10.7% versus 45.8% ± 8.8%, respectively ($p < 0.01$);†[33] values were 30.9% ± 11.4% versus 38.2% ± 9.1% for the comparison of children on treatment versus baseline within the treated group ($p < 0.001$).[34,35]

Virtually all these results should be treated with caution because many of the statistical comparisons are within-group before and after treatment comparisons, rather than comparisons between treated and untreated groups (see appendix 7).

Behavioural

Children treated with GH did not significantly differ from untreated children across a range of behaviours, including attention, depression, compulsion, anxiety, violence and psychoses.[36] There were also no group differences in symptoms associated with PWS, such as arguing, obsessional thoughts, destroying property and stealing food. There were significant within-group differences from baseline (improvements) in the GH-treated group in obsessional thoughts (baseline, 1.56; 12 months, 1.29; $p < 0.05$) and skin-picking (baseline, 1.38; 12 months, 1.08; $p < 0.05$). Given that behavioural problems are a characteristic of PWS, it was noted that GH treatment did not result in any apparent behavioural deterioration. Unfortunately, these behavioural measures are not appropriate for use in economic modelling.

Final height outcomes

One study involving a single group of 16 participants reported final height results.[52] The abstract reported that the boys achieved an average height of 170 ± 10 cm, and the girls achieved a height of 159 ± 4 cm. The final HtSDS was –0.2 ± 1.3 ($p < 0.0001$).

This study did not include a control group, and no controlled final height data were found. Therefore, as in GHD, the improvement due to GH treatment was presumed to be the change in HtSDS from the

* The statistical probability values from this trial should be interpreted with caution. The report indicates that the *p*-values are associated with **either** comparisons between treated and untreated groups, **or** comparisons between baseline and 12 months on treatment within the treatment group.

† Drug dose was given according to patient weight.

inception of treatment to the conclusion of treatment. The average HtSDS at the start was –1.84 ± 1.56. Therefore, the presumed treatment effect is 1.64 SD, or approximately 11 cm in boys and 9.8 cm in girls (for conversion, see footnote to *Table 1*).

Because this study did not involve a control group or a large number of participants, these effectiveness estimates should be considered with caution. The participants may not have been representative because they were within 2 SD of normal average heights at the start of treatment. However, it was noted that they also had documented GHD and therefore, as with other children with GHD, if left untreated, their height deficit may have become even greater by adulthood. If that were true, the estimated treatment effects may be an underestimate. It is also not known how many children with PWS also have GHD. This may be another reason to treat these results with caution because they may not be representative of other children with PWS.

Adverse effects

In one trial,[33] headaches developed in two patients within the first 3 weeks. Symptoms resolved with temporary cessation and gradual re-institution of GH. In another trial,[34,35] one boy developed low thyroxine levels without a change in the level of thyroid-stimulating hormone. He was treated with substitution L-thyroxine during GH treatment. Increased levels of fasting insulin were also noted in this study, although they remained within the normal range and declined after cessation of treatment. In the third trial,[5] one boy developed pseudotumour cerebri 2 weeks after increasing the starting dose. He tolerated half the standard dose. Among the patients treated for a longer period (5 years),[70] three patients developed hyperinsulinaemia when they were on a high dose of GH (0.47 mg/kg/week for 1 year). Two of these patients developed non-insulin-dependent diabetes mellitus after a rapid weight gain thought likely due to poor dietary compliance. After GH was stopped, their fasting glucose, insulin and glycosylated haemoglobin (HbA_{1C}) levels normalised.

Cost-effectiveness of GH in PWS

Model parameters and data

A model of the cost-effectiveness of GH treatment in PWS was populated with the best available evidence. *Table 3* in chapter 2 lists the model parameters that were common to all five conditions. The additional parameters that were specific to PWS are shown in *Table 28*. The effect of GH on short-term growth in children with PWS was taken from the effectiveness review above. Only one study analysed the impact of treatment on final height, but the validity and generalisability of the results are questionable (see base case 3).

TABLE 28 *Model parameters, values and data sources for GH in PWS*

Parameter	Value and source
Population data	
Sex distribution of patients	50% males (modeller's opinion)
Effectiveness data	
Base case 1:	
Length of treatment (assumes child aged 11 years)	5 years (modeller's assumption)
HtSDS – benefit uniformly spread over treatment period	1.4 HtSDS at 1 year[34,35]
Drug doses for condition	0.233 mg/kg/week[34,35]
Base case 2:	
Length of treatment (assumes child aged 8 years)	5 years (modeller's assumption)
HtSDS – benefit uniformly spread over treatment period	1.0 HtSDS at 1 year[33]
Drug doses for condition	0.35 mg/kg/week
Base case 3 (effectiveness measure of FH):	
Length of treatment (assumes child aged 8 years	8 years[52]
Final height gain – benefit uniformly spread over treatment period	10.38 cm (assessed[52] and based on the distribution of final height for general population)
Drug doses for condition	0.23 mg/kg/week[52]
Investigation and treatment parameters	
GH treatment drop-out rate after first year of treatment	0%[33]
Drop-out rate from monitoring after first year of monitoring	0%[33]

TABLE 29 *Scenarios for base cases 1 and 2: GH treatment in PWS*

Scenario	Description
Scenario A	Same parameter values as base cases, with the exception of the assumption about length of treatment, which is assumed to vary between 8 and 12 years
Scenario B	Same parameter values as base cases, with the exception of the assumption about drop-out rate, which is assumed to vary between 0% and 20%

The estimates of the cost and cost-effectiveness of using GH in PWS were modelled using the parameters above and two treatment scenarios (see *Table 29*). The scenarios describe important factors that influence successful treatment and the cost of treatment.

Costs, effects and ICERs

The costs of GH treatment and growth monitoring are based upon costs associated with the appropriate event pathway (see appendix 9). The event pathway for no GH treatment is depicted in diagram A of appendix 9. The event pathway for the decision as to whether to offer GH treatment and whether treatment will be accepted in PWS is depicted in diagram D. Diagram F depicts the event pathway for GH treatment in PWS. These event pathways specify the various parameters that must be included in order to realistically estimate the costs associated with GH treatment and no treatment (i.e. growth monitoring) in PWS.

Costs were estimated using the appropriate parameters specified from the event pathways and the treatment assumptions outlined in the scenarios above. *Table 30* reports estimates of mean discounted recurrent costs achieved under the assumptions of the base cases.

Table 31 reports the ICERs under the base cases. These ICERs reflect the incremental cost of treatment for each SD of short-term height gain with GH treatment over growth monitoring (no GH treatment).

Interpretation of the ICERs associated with changes in HtSDS in PWS is difficult. The meaning of the incremental effectiveness unit (HtSDS) is unclear. Furthermore, modelling has presented the results over treatment periods similar to those used for the other conditions, but the clinical evidence is less robust because it is limited to 1-year follow-up. If an assumption is made that the HtSDS at the end of treatment equals HtSDS at 1 year, the cost of

TABLE 30 *Estimates of mean discounted recurrent costs per patient with PWS undergoing GH treatment and growth monitoring (2000 prices)*

Condition: PWS	Mean total cost of GH treatment	Mean drug cost (% of total cost)	Mean cost of growth monitoring
Base case 1	£56,663	£54,620 (96%)	£1,210
Base case 2	£84,055	£82,012 (98%)	£1,210
Base case 3	£70,882	£68,208 (96%)	£1,620

TABLE 31 *Estimates of mean discounted ICERs per patient undergoing GH treatment for PWS (2000 prices)*

Condition: PWS	Mean incremental total cost per patient	Mean units gained per patient*	Incremental cost per unit gained (ICER)	Estimate of uncertainty range (minimum to maximum ICER)†
Base case 1	£55,453	1.36 HtSDS	£40,815 per HtSDS†	£10,873–121,341 per HtSDS†
Base case 2	£82,845	0.97 HtSDS	£85,368 per HtSDS†	£17,760–169,877 per HtSDS†
Base case 3	£69,263	9.85 cm in FH	£7,030 per cm	£1,466–20,897 per cm

* *HtSDS gains are 1-year effectiveness estimates. All effectiveness estimates were adjusted for drop-outs and gender (if data were available) and discounted*

† *One-way sensitivity analysis results (see appendix 10)*

TABLE 32 *Scenario analysis: estimates of mean discounted ICERs for PWS*

Scenario analysis	ICER estimate or range: base case 1	ICER estimate or range: base case 2	ICER estimate or range: base case 3
Scenario A	£52,130–57,985 per unit HtSDS	£109,025–121,188 per unit HtSDS	£7,030–7,820 per cm FH
Scenario B	£40,815–42,728 per unit HtSDS	£85,368–89,332 per unit HtSDS	£7,030–7,226 per cm FH
Maximum *BNF* price for drug therapy	£45,836 per unit HtSDS	£95,921 per unit HtSDS	£7,895 per cm FH

GH treatment of PWS children is between £40,815 and £85,368 for about one unit increase in HtSDS.

The cost of an additional centimetre gained in final height is £7030, but this estimate is sensitive to the estimate of the gain in final height.

In *Table 32,* ICERs are presented for scenarios that represent realistic treatment possibilities. The annual cost of GH treatment varies with the weight of the child. The annual treatment cost of a 30-kg child was between £7931 (GH dose of 0.233 mg/kg/week; 96% GH cost) and £11,749 (GH dose of 0.35 mg/kg/week; 97.3% GH cost).

Summary of effectiveness and cost-effectiveness of GH in children with PWS

- Three RCTs that included 54,[33,36] 27[34,35] and 16[5] participants included both children with PWS who were treated with GH and untreated children with PWS. The trials were all 1 year in duration. One single-cohort study reported final height in 16 treated children.[52]
- All RCTs received Jadad quality scores of 2/5. They were not double-blind and did not specify the means of randomisation or subject sampling. The final height study was reported in abstract form only, and therefore study quality could not be fully assessed. Also, it is not known whether the children in this study were representative of other children with PWS.
- One-year growth was greater on GH, resulting in treated children being approximately 1 SD taller than the untreated children. Short-term GV was also substantially greater in the treated than the untreated children.
- One abstract[52] reported final height in a small group of treated children with PWS. The study reported final height of 170 cm in boys and 159 cm in girls. These heights are well within the normal range. Presuming a treatment effect based on the change in SD from the start of treatment to the completion of treatment, there was an increase of 1.64 SD. Converting this SD improvement to centimetres in adult height, this corresponds to treated boys being approximately 11 cm taller and treated girls being approximately 9.8 cm taller than untreated children would presumably be. These results, however, should be treated with caution because there was no control group, the number of participants was small, the representativeness of the participants is not known, and certain assumptions have been made in estimating a treatment effect.
- Body composition was improved over the short term in children treated with GH. They had less fat (7–8%) and more lean body mass (approximately 4 kg) than untreated children.
- Children treated with GH did not differ from untreated children across a range of behaviours and psychological symptoms. There were small improvements from baseline within a GH-treated group in obsessional thoughts and skin-picking.
- Few serious adverse effects were noted. Among the children treated for 5 years, three developed non-insulin-dependent diabetes mellitus, although it was unclear whether this was attributable to GH treatment. After cessation of GH treatment, fasting glucose, insulin and HbA_{1C} levels normalised. Within the shorter trials, there was one case of pseudotumour cerebri, one case of low thyroxine levels and two cases of headaches. There are indications that children with PWS may have greater susceptibility to various adverse effects perhaps related to obesity.
- The results of the PWS cost-effectiveness model are difficult to interpret owing to difficulty in both understanding the meaning of a unit increase in HtSDS and extrapolating clinical data for 1-year follow-up over longer treatment periods.

- The incremental cost of GH treatment for one child with PWS (for 5 years) was estimated to be between £55,500 and £83,000.
- The incremental cost of a gain of 1 SDS in height (prior to the completion of growth) due to GH treatment (ICER) after 5 years of treatment could be in the range of £40,800–85,400, but could range from £10,873 to £169,877. The assumption that the gain of 1 SDS in height that was seen in the first year of GH treatment in the effectiveness studies is all that would be realised over 5 years of treatment may not be valid.
- The incremental cost of each centimetre gained in final height was £7030, but this estimate is based on a single study of questionable validity and generalisability.
- The annual cost of GH treatment of a 30-kg child was between £8000 and £11,800, and the cost of treatment monitoring was not more than 4% of the annual cost.

Chapter 8

GH in idiopathic short stature

Background

ISS is the term used when children are very short (i.e. 2 or more SD below normal height) compared with others in their age cohort, for unknown or hereditary reasons. This group is heterogeneous, made up of patients whose short stature cannot be explained by an underlying pathology and who meet the following minimal criteria:

- normal size for gestational age at birth
- normal body proportions
- no evidence of endocrine deficiency
- no evidence of chronic organic disease, no psychiatric disease or severe emotional disturbance, and normal food intake
- slow or normal GV throughout the growth process.

By definition, children with ISS do not have a disease. Consensus of expert opinion[71] has concluded that ISS can be divided into two sub-categories: familial short stature (FSS) and non-familial short stature (NFSS). These two categories may be further subdivided into constitutional growth delay (CGD) and non-constitutional growth delay (NCGD). CGD is a term that describes a temporary delay in the skeletal growth and height of a child, with no apparent physical abnormalities causing delay. CGD may be a result of a growth pattern inherited from a parent (familial) or may occur for no apparent reason (sporadic). Children with CGD usually attain an adult height that falls within the normal range. The only subclassifications of ISS that may be made with certainty before puberty are FSS and NFSS, which can be further subdivided into CGD and NCGD only after puberty onset.

Because of the arbitrary cut-off point of a peak GH level of 10 µg/l, it is probable that some patients labelled GHD could be categorised as having ISS, and conversely some individuals currently labelled as having ISS may have GHD.

Use of GH in ISS

GH is not licensed in the UK for treatment of children with ISS, and the number of children with ISS being treated has not been separated from other unlicensed indications; however, it has been estimated that at most approximately 275 children with ISS may be receiving treatment[8] (see *Table 2*).

The doses of GH used are usually higher than those for children with GH insufficiency at 0.33 mg/kg/week (9–10 mg/m^2/week).[16]

Quality and quantity of effectiveness studies

Eight RCTs and two non-RCTs met the inclusion criteria (*Table 33*).

RCTs

Eight RCTs met the inclusion criteria for the review (*Tables 33* and *34*, with details in appendix 19).

The studies had small sample sizes, and only three studies[38,42,43] included more than 50 participants. Inclusion criteria for participants were broadly similar, specifying short normal children less than the 3rd percentile in height, with no chronic illness or dysmorphic syndromes. Five studies[23,38–40,43] included children who were prepubertal, and two studies[37,41] had pubertal children, one of which included girls only.[37]

Six of the trials[23,37–41] compared GH-treated children with untreated controls, with an additional treatment group receiving luteinising hormone-releasing hormone analogue (LHRHa) to delay puberty in one trial,[41] and an additional group of patients who did not give consent to randomisation in another trial.[37] Two studies[42,43] were placebo controlled, with an additional observation group in one.[43] Two of the three earlier trials used a dose of 0.3 mg/kg/week,[38,43] and one used either 0.2 or 0.4 mg/kg/week.[42] The later studies computed doses based on body surface area. Doses ranged from low doses of 5 mg/m^2/week[23] and 5.33 mg/m^2/week[41] to higher doses of 6.67 or 13.33 mg/m^2/week,[40] and 10 mg/m^2/week.[37,39]

Only one study had a follow-up time long enough to report near final height.[37] All the other studies were short term and reported short-term outcomes

TABLE 33 *Summary of study details: ISS*

Reference	Control group	Intervention	Participants	Duration
McCaughey *et al.*, 1998[37] Jadad score: 2/5	Randomised and declined treatment*	GH vs no treatment (and non-consent) GH: 10 mg/m^2/week	10 (GH) 8 (no treatment) 22 (non-consent) All girls with height ≥ 2 SD below mean	6 years
Genentech, 1989[38] Jadad score: 1/5	Randomised	GH vs no treatment GH: 0.3 mg/kg/week	63 (GH) 58 (no treatment) All prepubertal children with peak GH ≥ 10 µg/l	1 year
McCaughey *et al.*, 1994[39] Jadad score: 2/5	Randomised	GH vs no treatment GH: 10 mg/m^2/week	21 (GH) 20 (no treatment) All prepubertal children with peak GH > 15 mU/l	3 years
Soliman & Abdul-Khadir, 1996[23] Jadad score: 2/5	Randomised	GH vs no treatment GH: 5 mg/m^2/week	12 (GH) 12 (no treatment) All prepubertal children with peak GH > 10 µg/l	1 year
Barton *et al.*, 1995[40] Jadad score: 2/5	Randomised	GH vs no treatment GH: "standard" dose, 6.67 mg/m^2/week; "high" dose, 13.33 mg/m^2/week	10 (GH, standard dose) 10 (GH, high dose) 9 (no treatment) All prepubertal children	1 year
Volta *et al.*, 1993[41] Jadad score: 1/5	Randomised	GH vs no treatment vs GH + LHRHa (last group not reported) GH: 5.33 mg/m^2/week	6 (GH) 6 (no treatment) All pubertal children with peak GH > 10 ng/ml	1 year
Cowell, 1990[42] Jadad score: 2/5	Randomised	GH (low dose) vs GH (high dose) vs placebo GH: low dose, 0.2 mg/kg/week; high dose, 0.4 mg/kg/week	37 (GH, low dose) 40 (GH, high dose) 27 (placebo) All children with peak GH > 20 mU/l	6 months
Ackland *et al.*, 1990[43] Jadad score: 3/5	Randomised	GH vs placebo vs observation GH: 0.3 mg/kg/week	30 (GH) 28 (placebo) 31 (observation) All prepubertal children with peak GH ≥ 15 mU/l	6 months
Zadik *et al.*, 1992[53]	Declined treatment	GH vs no treatment GH: 0.25 mg/kg/week	11 (GH) 17 (no treatment) All peripubertal boys with peak GH > 10 µg/l	≥ 4 years
Hindmarsh & Brook, 1996[54]	Declined treatment	GH vs no treatment GH: 4.07–7.0 mg/m^2/week for 2 years, then 6.67 mg/m^2/week	16 (GH) 10 (no treatment) All short normal children	7.5 years

LHRHa, luteinising hormone-releasing hormone analogue

* *The group declining treatment was included because statistical comparisons were made between the treated group and the randomised untreated group combined with the group who declined treatment*

TABLE 34 *Summary of study results assessing the effectiveness of GH in ISS*

Reference	Outcome (mean)	GH		Placebo or no treatment		Statistical comparison GH vs control
		After treatment	Δ	After	Δ	
RCTs						
McCaughey *et al.*, 1998[37]	NFH (cm)	155.3		Control: 147.8 Non-consent: 149.3		$p = 0.003$ (GH vs control + non-consent)
	NF HtSDS	–1.14		–2.37 –2.13		$p = 0.004$ (GH vs control + non-consent)
McCaughey *et al.*, 1994[39]	HtSDS	–1.2	+1.2 (3 years)	–2.4	0.0	$p < 0.001$
Soliman & Abdul-Khadir, 1996[23]	HtSDS	–1.7	+0.85*	–2.6	+0.2	$p < 0.05$
Barton *et al.*, 1995[40]	HtSDS	Standard dose: –1.7† High dose: –1.2†	+0.4 +0.8	–2.1	+0.1	NS
Volta *et al.*, 1993[41]	HtSDS	1.7	+3.9*	–2.2		NS
Genentech, 1989[38]	GV (cm/year)	Prepubertal: 7.3 Pubertal: 8.4	+2.6* +4.1	4.7 6.0	+0.3 +2.5	$p < 0.00005$ $p < 0.001$
McCaughey *et al.*, 1994[39]	GV (cm/year)	6.4 (year 3)		5.2 (year 3)		$p < 0.003$
Soliman & Abdul-Khadir, 1996[23]	GV (cm/year)	7.6	+3.4*	5.5	+1.0	$p < 0.05$
Volta *et al.*, 1993[41]	GV (cm/year)	8.0	+3.7*	6.6	+1.9*	
Cowell, 1990[42]	GV (cm/6 months)	Low dose: 8.7 High dose: 10.8		5.3		"significant" (no *p*-value)
McCaughey *et al.*, 1994[39]	GVSDS	0.74 (year 3)		–0.25 (year 3)		
Barton *et al.*, 1995[40]	GVSDS	Standard dose: 2.71† High dose: 5.66†	+3.3 +5.91	–0.48	–0.03	$p < 0.001$
Volta *et al.*, 1993[41]	GVSDS	3.9 (for BA)	+4.8*	0.4 (for BA)	+1.7*	$p < 0.05$
Ackland *et al.*, 1990[43]	GVSDS (6 months)	1.98	+3.24*	Placebo: –0.63 Observation: –0.87	+0.66* –1.96	$p < 0.0001$
Non-RCTs						
Zadik *et al.*, 1992[53]	FH (cm)	164.5		157.6		$p < 0.04$
	Final HtSDS	–1.5		–2.7		$p < 0.04$
Hindmarsh & Brook, 1996[54]	FH increment (cm)	Boys: 2.8 Girls: 2.5				

Δ, *change from baseline; NF, near final*

* *Within-group before/after comparison was statistically significant*

† *Median*

such as GV or HtSDS at baseline to 6 months,[42,43] or baseline to 1 year[23,38,40,41] or 3 years.[39]

Jadad quality assessment scores for all studies were ≤ 3/5. Only one of the trials[43] received a score of 3/5, but it did not describe the randomisation method used or give details of withdrawals. All of the five trials[23,37,39,40,42] receiving scores of 2/5 did not describe the method of randomisation used, four trials lacked any mention of blinding,[23,37,39,40] and one trial[42] did not give details of blinding or withdrawals. The trials receiving scores of 1/5 did not give adequate description of randomisation, did not mention blinding, and did not clearly describe drop-outs and withdrawals.[38,41]

Studies reporting final height

Two non-randomised studies[53,54] reporting final height met the inclusion criteria for the review (*Tables 33* and *34*, with details in appendix 20).

One study was a small, open study of consecutive referrals to a growth disorder clinic, and GH doses ranged from 4.07–7.00 mg/m^2/week in the first 2 years to 6.67 mg/m^2/week thereafter, with controls being children who declined treatment.[54] The other study[53] was a small prospective cohort study with concurrent controls, and included boys with ISS and a subnormal integrated concentration of GH (IC-GH < 3.2 µg/l). These children are considered by some clinicians to be a separate diagnostic category. The treated group received a GH dose of 0.25 mg/kg/week.

In one study,[54] proper sampling was used, criteria for outcomes were objective and verifiable, there was blind assessment of outcomes, groups were comparable, attrition rates were reported, and results are likely to be generalisable. In the other study,[53] objective criteria for outcomes and inclusion were used, and the two groups were comparable.

Assessment of effectiveness of GH in ISS

Results suggest that GH is effective in promoting growth in ISS, with significant changes in HtSDS and GV, and increased final height after GH treatment (*Table 34*).

Short-term outcomes

HtSDS

In the McCaughey trial,[39] HtSDS in GH-treated prepubertal children with ISS changed from –2.4 to –1.2 at 3 years, compared with no change from –2.4 in untreated controls ($p < 0.001$). In the Soliman trial,[23] a change in HtSDS was also shown after 1 year of GH treatment in prepubertal children, from –2.55 ± 0.5 to –1.7 ± 0.45 in the GH-treated group, compared with a change from –2.8 ± 0.96 to –2.6 ± 0.9 in untreated controls ($p < 0.05$). The Barton trial[40] testing prepubertal children found no significant differences in HtSDS between treated and untreated children after 1 year, even when considering a high dose of GH (40 IU/m^2 per week). In the Volta trial,[41] a significant change in HtSDS from baseline was reported after 1 year of GH treatment in pubertal children in whom HtSDS changed from –2.2 ± 0.2 to –1.7 ± 0.2 ($p < 0.05$), compared with no change in untreated controls or those children receiving LHRHa. It is noteworthy that these were within-group comparisons and that there were no significant differences between the groups.

GV

The McCaughey study,[37] which considered near final height in girls, found no difference in GV between treated and untreated groups ($p = 0.21$). The increase in GV from baseline to 1 year in prepubertal children (4.7 ± 1.2 to 7.3 ± 1.2 cm/year, $p < 0.00005$) and pubertal children (4.3 ± 0.8 to 8.4 ± 0.9 cm/year, $p = 0.001$) treated with GH was significantly greater than in untreated controls in the Genentech study.[38] In another study,[39] a significant difference in GV at 3 years was found between GH-treated prepubertal children and untreated controls: 6.4 cm/year versus 5.2 cm/year, respectively ($p < 0.003$). The Soliman study[23] also reported GV significantly greater after 1 year of GH treatment (from 4.2 ± 0.9 to 7.6 ± 1.2 cm/year) compared with the control group (from 4.5 ± 1.6 to 5.5 ± 1.5; GH vs control, $p < 0.05$). The Volta study[41] reported GV after 1 year, with a significant increase in pubertal children treated with GH (from 4.4 ± 0.3 to 8.0 ± 1.0 cm/year; $p < 0.05$), and untreated controls also showing a smaller but significant increase (from 4.7 ± 0.4 to 6.6 ± 0.6; $p < 0.05$), attributed by the authors of the study to the beginning of the pubertal growth spurt in some controls. It is noteworthy that these are within-group before and after comparisons, rather than between-group comparisons. Cowell[42] reported that GV was significantly increased after only 6 months of GH treatment, compared with placebo (no *p*-value reported).

GVSDS

GVSDS showed a significant increase in GH-treated children at 1 year in prepubertal children ($p < 0.001$)[40] and pubertal children ($p < 0.05$)[41] compared with untreated controls, and at

6 months in prepubertal children compared with those receiving placebo ($p < 0.0001$).[43]

Final height outcomes

Near final height

McCaughey and co-workers[37] reported that near final height was significantly greater after GH treatment in a study of pubertal girls in which the GH group was 7.5 cm and 6.0 cm taller than the two control groups (untreated controls and the group that did not give consent to randomisation), respectively (GH group, 155.3 ± 6.4 cm; control group, 147.8 ± 2.6 cm; non-consent group, 149.3 ± 3.3 cm; $p = 0.003$ for GH group vs control and non-consent groups).

Near final HtSDS was significantly greater after GH treatment. Near final HtSDS for GH-treated girls was –1.14 ± 1.06, compared with –2.37 ± 0.46 in the control group and –2.13 ± 0.55 in the group not consenting to randomisation ($p = 0.004$ for GH group vs control and non-consent groups).[37]

Final height

The Zadik non-randomised study,[53] which considered boys with subnormal IC-GH, found a significantly greater final height in the GH-treated group compared with untreated controls: 164.5 ± 3.9 cm versus 157.6 ± 4.5 cm, respectively ($p < 0.04$). The Hindmarsh and Brook study[54] found an average height increase in GH-treated children of 2.8 cm in boys and 2.5 cm in girls.

Final HtSDS

Final HtSDS for GH-treated boys was –1.5 ± 0.6, compared with the control group's final HtSDS of –2.7 ± 0.7 ($p < 0.04$), and GV was significantly greater in GH-treated children than untreated controls ($p = 0.001$).[53]

Adverse effects

No serious adverse effects were reported in the included studies. One trial[39] reported that children in the GH-treated group were relatively hyperinsulinaemic, with their mean fasting insulin levels significantly greater than those in the untreated group: 66.7 ± 13.8 versus 44.5 ± 7.2 pmol/l, respectively ($p < 0.01$).

Cost-effectiveness of GH in ISS

Model parameters and data

A model of the cost-effectiveness of GH treatment in ISS was populated with the best available evidence. *Table 3* in chapter 2 lists the model parameters that were common to all five conditions. The additional parameters that were specific to ISS are shown in *Table 35*. The effect of GH on final height in children with ISS was taken from the effectiveness review above.

The estimates of the cost and cost-effectiveness of using GH in ISS were modelled using the parameters above in the context of three treatment scenarios (see *Table 36*). The scenarios describe important factors that influence successful treatment and the cost of treatment.

TABLE 35 *Model parameters, values and data sources for GH in ISS*

Parameter	Value and source
Population data	
Sex distribution of patients	60% males (modellers' opinion)
Effectiveness data	
Base case 1:	
Length of treatment (assumes child aged 10 years)	6 years[37]
Final height gain – benefit uniformly spread over treatment period	7.5 cm[37]
Drug dose	0.35 mg/kg/week (30 IU/m^2/week;[37] 0.35–0.70 mg/kg/week[61])
Base case 2:	
Length of treatment (assumes child aged 9 years)	7 years[54]
Final height gain – benefit uniformly spread over treatment period	2.68 cm[54]
Drug dose	0.233 mg/kg/week (20 IU/m^2/week;[54] 0.35–0.70 mg/kg/week[61])
Investigation and treatment parameters	
GH treatment drop-out rate after first year of treatment	29%[39]
Drop-out rate from monitoring after first year of monitoring	30%[39]

TABLE 36 *Scenarios for base cases 1 and 2: GH treatment in ISS*

Scenario	Description
Scenario A	Same parameter values as either base case, with the exception of the assumption about length of treatment, which is assumed to vary between 5 and 12 years
Scenario B	Same parameter values as either base case, with the exception of the assumption about drop-out rate, which is assumed to vary between 0% and 20%
Scenario C	Same parameter values as either base case, with the exception of the administration of drug dose, which is based on age- and sex-related weight at the 9th percentile

Costs, effects and ICERs

The costs of GH treatment and growth monitoring are based upon costs associated with the appropriate event pathway (see appendix 9). The event pathway for no GH treatment is depicted in diagram A of appendix 9. The event pathway associated with investigating ISS is depicted in diagram B, and the event pathway for the decision as to whether to offer GH treatment and whether treatment will be accepted in ISS is depicted in diagram C. Diagram F depicts the event pathway for GH treatment in ISS. These event pathways specify the various parameters that must be included in order to realistically estimate the costs associated with GH treatment and no treatment (i.e. growth monitoring) in ISS.

Costs were estimated using the appropriate parameters specified from the event pathways and the treatment assumptions outlined in the scenarios above. *Table 37* reports estimates of mean discounted recurrent costs achieved under the assumptions of both base cases.

Table 38 reports the ICERs under both base cases. These ICERs reflect the incremental cost of treatment for each centimetre in final height gained with GH treatment over growth monitoring (no GH treatment).

In *Table 39*, ICERs are presented for scenarios that represent realistic treatment possibilities.

TABLE 37 *Estimates of mean discounted recurrent costs per patient with ISS undergoing GH treatment and growth monitoring (2000 prices)*

Condition: ISS	Mean total cost of GH treatment	Mean drug cost (% of total cost)	Mean cost of growth monitoring
Base case 1	£70,674	£68,155 (96%)	£1,440
Base case 2	£51,023	£48,316 (95%)	£1,535

TABLE 38 *Estimates of mean discounted ICERs per patient undergoing GH treatment for ISS (2000 prices)*

Condition: ISS	Mean incremental total cost per patient	Mean cm gained per patient*	Incremental cost per cm gained (ICER)	Estimate of uncertainty range (minimum to maximum ICER)†
Base case 1	£69,234	5.13 cm	£13,498 per cm	£4,295–134,978 per cm
Base case 2	£49,488	1.82 cm	£27,202 per cm	£8,096–272,019 per cm

* *Adjusted for drop-outs and gender (if data were available) and discounted*
† *One-way sensitivity analysis results (see appendix 10)*

TABLE 39 *Scenario analysis: estimates of mean discounted ICERs for ISS*

Scenario analysis	ICER estimate or range: base case 1	ICER estimate or range: base case 2
Scenario A	£12,292–16,695 per cm	£23,086–31,414 per cm
Scenario B	£12,697–13,187 per cm	£25,789–26,654 per cm
Scenario C	£10,914 per cm	£22,065 per cm
Maximum *BNF* price for drug therapy	£15,157 per cm	£30,518 per cm

The annual cost of GH treatment varies with the weight of the child. The annual treatment cost of a 30-kg child was between £7931 (GH dose of 0.23 mg/kg/week; 2.7% monitoring costs) and £11,800 (GH dose of 0.35 mg/kg/week; 4% monitoring cost).

Summary of effectiveness and cost-effectiveness of GH in children with ISS

- The effects of GH in children with ISS have been reported from eight published RCTs and two published non-RCTs reporting final height.
- The children who are considered in studies of ISS are quite heterogeneous, and therefore generalisations are difficult.
- The published RCTs received Jadad quality scores ≤ 3/5. All but one of the studies were short term, with one small study reporting near final height in girls.
- Results from the published RCTs suggest that GH therapy is effective in promoting growth in children with ISS in the short term, and significant improvements can be achieved when assessed using HtSDS and GV measures.
- One RCT reported near final height in girls. Two published studies reporting final height were prospective non-RCTs, one in peripubertal boys with subnormal IC-GH and one in short normal children.
- Results from the RCT including near final height found that treated girls were approximately 7.5 cm taller than girls randomised to the control group and 6 cm taller than girls who refused consent. Other long-term studies also suggest that final height is increased by GH treatment. However, the increase is between 2 cm and 7 cm, and treated individuals remain relatively short when compared with peers of normal stature.
- No serious adverse effects of treatment have been reported.
- The incremental cost of GH treatment for one child with ISS was estimated to be between £50,000 and £70,000.
- The annual cost of GH treatment of a 30-kg child was between £8000 and £11,800, and the cost of treatment monitoring was no more than 4% of the annual cost.
- The incremental cost of each centimetre in final height gained due to GH treatment (ICER) was between £13,500 and £27,200, but could range from £4295 to £272,019.

Chapter 9
Safety of GH

The included trials reported few adverse effects of GH in the relatively small numbers of children tested. This indicates that serious adverse effects are not common. However, rare but potentially important adverse effects may not be detected in the context of such small trials. Most of the included studies had approximately 50 participants. In such trials reporting no serious adverse effects, the upper confidence limit for serious adverse effects would be approximately 6%.

Large databases of GH use and voluntarily reported adverse effects are kept by two pharmaceutical companies: the Pharmacia International Growth Database, known as KIGS (Pharmacia Corporation, Stockholm, Sweden), and the National Cooperative Growth Study (NCGS; Genentech, South San Francisco, California, USA). These databases form the primary information about the safety of GH in children. However, it should be noted that, because of voluntary reporting to these databases, adverse effects may be under-reported. Adverse effects reported to these databases are summarised below. The two reports[72,73] included data collected up to 1996, and included approximately 19,000 patients registered in NCGS and 20,000 patients registered in KIGS. The likelihood of particular adverse effects also varies according to the diagnosis of the children being treated.

The adverse effects that are most serious and warrant careful continued evaluation, both in individuals and in the treated population, are diabetes mellitus, slipped capital femoral epiphyses and malignancies. Particular attention should be paid to treating children with risk factors associated with these disorders.

- **Diabetes mellitus**: A primary safety concern has been the possibility of increased risk of diabetes mellitus. GH does contribute to insulin resistance. Cutfield and co-workers[74] evaluated the KIGS database and reported no increased risk of type 1 diabetes mellitus with GH treatment, but a six-fold higher incidence of type 2 diabetes mellitus in children treated with GH. It has been suggested that GH may accelerate the disorder in predisposed individuals.[73,74] Other reports have concluded that the risk of permanent diabetes mellitus in GH-treated children is no higher than in the normal population.[72]
- **Slipped capital femoral epiphyses**: In KIGS, approximately 0.33 cases of slipped capital femoral epiphyses per 1000 treatment-years were found. This is a higher risk than in the general population. The risk seems particularly great in GH-treated children who had been treated for leukaemia.[73] There seems also to be a higher risk in children with GHD and TS.[75]
- **Neoplasms**: There have been concerns that GH would induce new tumours or increase the likelihood of tumour relapse. Reports suggest that the risk of new tumours or tumour recurrence is not elevated in children treated with GH who have no other increased risk factors.[16,72,73,76]
- **Growth of naevi**: GH treatment may increase the number, size or pigmentation of naevi, but does not appear to increase the risk of malignancy.[72]
- **Idiopathic intracranial hypertension** (IIH): Reports indicate that perhaps approximately 1 in 1000 children treated with GH will suffer from IIH.[72,76] Of these children, it may be important to differentiate between those who develop this condition shortly after beginning GH treatment, and those whose symptoms appear much later and in whom there is less evidence that IIH is due to GH. IIH is more likely in children with renal disease,[77] GHD, TS or obesity.
- **Oedema and lymphoedema**: Fewer than 0.1% of children treated with GH develop symptomatic oedema. Those in whom it developed early in treatment (most likely attributable to treatment) had a previous history of lymphoedema and were more likely to have TS.[72]
- **Carpal tunnel syndrome**: Fewer than 0.05% of children treated with GH were reported to have carpal tunnel syndrome. Of these, approximately half had symptoms prior to treatment.[72]
- **Gynaecomastia**: Gynaecomastia has been reported in a small number of prepubertal boys. Although this risk seems slightly elevated, the condition is benign and self-limiting.[72,73]
- **Development of antibodies to GH**: A few patients develop antibodies to GH, which are generally of no clinical significance. In some

patients, the development of antibodies to GH can be associated with growth rate deceleration.[72]
- **Hypothyroidism**: GH may unmask incipient hypothyroidism.[16]
- **Scoliosis**: Children with TS and PWS are at increased risk of scoliosis. Accelerated rates of growth may exacerbate scoliosis.[78]

Many reported adverse effects seem to occur in GH-treated individuals with no greater frequency than they would in the normal population, or they seem to be associated with known risk factors in many of those affected. Often, adverse effects can be managed by transient reduction of the GH dose or temporary discontinuation of GH.[16]

It should also be noted that the requirement that GH be injected daily is not trivial. The injections are inconvenient and can be painful, although delivery systems have been developed to lessen discomfort. These factors can have a serious impact on compliance. Low levels of compliance could lessen effectiveness and would affect cost-effectiveness. Because of the long-term nature of trials and the fact that GH is administered at home, it is assumed that compliance outside trials would not be significantly different than within trials, and therefore the current evidence is based on a realistic level of compliance.

In addition, it has been noted that years of daily injections may have psychological implications, for instance, suggesting to children that there is something wrong with them.[69] In addition, they may develop unrealistic expectations about the potential effects of GH treatment.[69]

In summary, serious adverse effects are rare; however, those children with other risk factors for serious disorders (e.g. diabetes mellitus) should be carefully monitored.[78]

Chapter 10

Optimal treatment strategies

As is clear from the summaries of included studies, the dose of GH given varies, not only between conditions, but within conditions. In addition, the age at which GH treatment is begun has varied across studies and is, of course, dependent upon when a child is diagnosed. The specific conditions that will optimise growth and final adult height in children have not been systematically evaluated via RCTs.

Evaluation of optimal treatment strategies presumes that GH is clinically effective and that treatment is undertaken. Rather than making these assumptions, the studies included in this review were chosen to answer the primary question of effectiveness. Different trial designs, which generally do not address the basic question of effectiveness but instead presume effectiveness, are required to address the question of optimal treatment. Insufficient evidence exists regarding the range of possible doses and the periods and duration of treatment to make definitive statements about treatment strategies. In addition to the wide range of possible treatment conditions that need to be tested against one another, these conditions would need to be maintained to final height to make any firm conclusions. Given the relative dearth of good-quality effectiveness information that reports final height, the raft of possible treatment combinations has certainly not been evaluated thoroughly.

Methods to assess optimal treatment strategies

The current report has focused upon an evaluation of the effectiveness of GH. Therefore, systematic searches and assessment of the literature were not undertaken to find studies of optimal treatment with GH. However, some suggestions as to optimal treatment are available in the studies that were used in the assessment of effectiveness. Some of the included trials have reported the results of regression analyses that are suggestive of the factors that affected growth within those studies. Within the studies included for the assessment of effectiveness, the factors discussed below have been reported to affect growth under GH treatment for the specified conditions.

GHD

GV after 1 year of GH therapy for GHD was significantly negatively correlated with GV before starting therapy and with GH peak response to provocation, and positively with the GH dose.[23]

One study[44] found that mid-parental HtSDS, GH dose frequency, treatment duration and GVSDS over the first year were all positively correlated with final height. Age and peak stimulated GH concentration were negatively correlated with final height.

TS

One trial found a significant positive correlation between height gain and age at the start of GH treatment in patients with TS.[48] Another study[46] reported that final HtSDS in GH-treated girls was positively correlated with HtSDS and bone age at baseline, maternal height, target height and birth weight. A third study reported a marginally significant negative correlation between height gain and pretreatment projected height, suggesting that shorter girls responded better than taller girls.[47]

Renal disease

It has been reported that short-term growth response to GH was greater in children with renal disease who had greater pretreatment GV and in children who were younger.[30] In another study treating children to final height, the change in height in centimetres was greater in children with a greater initial height deficit, in children with longer GH therapy and in children who spent less time on dialysis.[50] When height gain was assessed in SDs, a longer duration of GH therapy was also significantly correlated with height gain.[50]

ISS

In children with ISS, GV after GH treatment was significantly negatively correlated with pretreatment GV and with the GH peak

response to provocation.[23] A short-term trial found a strong relationship between change in GV during the first 3 months of GH treatment and that during the first 6 months, with approximately 90% of GV changes in the first 3 months being predictive of subsequent growth response.[42] There was a negative correlation between GV response and age.[42] In multiple regression analysis in one study,[54] the only factor significantly determining the difference in final HtSDS compared with pretreatment predicted HtSDS was the change in GVSDS during the first year of therapy, which was related to the dose of GH but not the age of the child (i.e. the most important factor that determined final height was the dose-dependent acceleration during the first year of therapy).

It should be noted that most of the included trials tested relatively small numbers of participants. These conditions can produce spurious correlations.

Starting and stopping GH treatment

The following observations regarding starting and stopping GH treatment were made within the context of the included trials.

One RCT[43] testing GH in children with ISS included an observation period during the discontinuation of GH after 6 months of treatment. Upon discontinuation, all groups had a significant drop in GVSDS, which returned to pretreatment levels. However, they did not have catch-down growth, which refers to the growth rate seen following a period of accelerated growth. During catch-down growth, GV falls to levels below those seen prior to acceleration so that height returns to its previous percentile.

One included study testing GH treatment in PWS assessed growth for 6 months following cessation of treatment.[34] This follow-up was after the point at which the control group had been discontinued, and therefore results should be interpreted with caution. Height velocity after GH was stopped was noted to "decline dramatically".[34] However, statistical comparisons were not included.

Professional guidelines

Guidelines from professional associations have focused on summarising the limited evidence on the effectiveness of GH in various conditions.[16,61,69,79,80] Professional societies have also made some treatment recommendations that are summarised briefly in *Table 40*.

Summary of optimal treatment strategies

Although limited evidence on optimal treatment strategies is available, if treatment is to be conducted, some speculative generalisations are possible. There are indications that short-term GV in children on GH is greatest in those whose pretreatment GV was highest and in younger children. Final heights seem greatest in those who were taller and predicted to be taller at baseline. Final height **gains** seem greatest in those who were shorter at baseline and who had a longer course of GH therapy. The distinction between results considering absolute final height or GV and gains in final height or GV points up the difference between outcome measures. Generally, absolute height or growth will be greatest in those who are already taller or growing most quickly, whereas gains may be greatest in those who start with the greatest deficit in height or growth.

Most indications are that treatment should be started as early as is feasible and continue until final height is achieved. It is ideal to maximise the height gained prior to puberty. Although height gains seem to be greatest in the first year or two of treatment, stopping treatment before achieving final height generally leads to loss of growth gains; however, this may not be the case in children with a well-functioning renal allograft. There is little information on the relationship between GH dose and growth response. Long-term safety has not been evaluated for very high GH doses.

TABLE 40 *Guidelines on the use of GH issued by some professional associations*

Professional body	Indication	Basic diagnostic criteria*	GH dose recommended	Start/stop recommendations
BSPED[16]	GHD	GH < 10 µg/l (or lower depending on test) IGF-I and/or IGFBP-3 < –2 SD (but may be normal)	25–50 µg/kg/day (0.175–0.35 mg/kg/week). In obese patients, consider dose by m^2	***Start***: at diagnosis
American Academy of Pediatrics[69]	GHD	GH < 10 µg/l with delayed BA and slow growth	Starting dose: 0.1 mg/kg/week	
Lawson Wilkins Pediatric Endocrine Society[80]	GHD	BA-specific GV < 25th percentile and delayed BA; rule out other GH suppression	0.15–0.3 mg/kg/week	***Adequate clinical response***: doubling of pretreatment GV in first year or increase in GV of ≥ 3 cm/year in children with extremely low pretreatment GV ***Stop***: at acceptable height or GV < 2.5 cm/year
AACE[64]	GHD		0.15–0.3 mg/kg/week in 6–7 subcutaneous injections	***Stop***: at final height or epiphyseal closure or both, or patient is no longer responding to treatment
BSPED[61]	TS		Not specified, but recommend relatively high doses	***Start***: ≤ 8 years of age
AACE[64]	TS		Commonly 0.375 mg/kg/week (usually divided into daily doses), often with OX, 0.0625 mg/kg daily. Low doses of oestrogen replacement until adequate growth achieved	***Start***: based on individual height and growth – often height < 5th percentile or HtSDS < –2 SD
AACE[64]	CRF		0.35 mg/kg/week in 6–7 doses	
BSPED[79]	Non-licensed indications		Usually 0.33 mg/kg/week, sometimes higher	"1. Treatment should only be undertaken in specialist centres that regularly participate in national audit of their clinical activities. 2. Any potential benefits and adverse medical events of therapy are discussed fully with the parents and child prior to treatment. 3. Response to treatment is carefully monitored, and the need for ongoing treatment re-evaluated annually."

IGFBP, insulin-like growth factor binding protein

* *Because of problems in the interpretation of GH secretion tests, all recommendations are to consider, not only GH secretion, but also auxological and clinical criteria*

Chapter 11

Research in progress

A great deal of research on GH is currently underway. Much of this research is considering GH doses, combinations of GH with other interventions and so on. However, there is some important research that will address the basic question of the effectiveness of GH therapy. Given that the inclination within the research community has been to not include placebo or no-treatment control groups, trials that include these groups and are continued to final height are important to consider. A few such trials are ongoing.

GH in TS

A meta-analysis of the effects of GH on final height is being conducted. It is expected that the analysis will be published in due course.

A randomised trial of GH versus no treatment in children with TS is virtually complete in Canada. Preliminary results are summarised in this report.[24]

A randomised, double-blind, placebo-controlled trial of GH in TS is being conducted under the sponsorship of the National Institute of Child Health and Human Development in the USA. This trial is no longer recruiting but will run for another 3–5 years for all participants to reach final height. This trial is also testing the effects of low-dose oestrogen (prior to the induction of puberty) on final height.

GH in CRF

A meta-analysis of RCTs of GH in CRF has been completed since this review was written.*

Although not a trial, the UK Renal Registry is now keeping information on the use of GH in children being treated for CRF. In addition, the growth of these children will be monitored in the registry.

GH in ISS

An RCT sponsored by the US National Institute of Child Health and Human Development has considered GH versus placebo in children with non-GH-deficient short stature. The trial stopped recruiting participants early due to slow accrual of data, and results are expected to be published in due course.

* Vimalachandra D, Craig JC, Cowell C, Knight JF. Growth hormone for children with chronic renal failure. *Cochrane Database Syst Rev* 2001;(4):CD003264.
Vimalachandra D, Craig JC, Cowell C, Knight JF. Growth hormone treatment in children with chronic renal failure: a meta-analysis of randomized controlled trials. *J Pediatr* 2001;**139**:560–7.

Chapter 12

Implications for other parties

Implications for the NHS

GH is licensed for use in GHD, CRF, TS and PWS. The number of prescriptions compared with the estimated prevalence of these conditions suggests that substantial proportions of potential patients are not receiving GH. The budgetary impact of extending the uptake of GH treatment among the licensed indications could be significant if treatment of the maximum number of potential beneficiaries is considered. The tendency to offer GH treatment earlier (i.e. increase the length of treatment) increases the cost of treatment per patient.

Considering primarily the licensed indications, the demands upon endocrinologists and others involved in prescribing and monitoring GH are not expected to change dramatically. However, if large numbers of children with ISS were to seek GH treatment, then these resources would be put under considerable stress, because there are many more children with ISS than children with licensed conditions.

Budgetary impact

This review's analysis of the budgetary impact of GH treatment aims to incorporate the current practice of GH treatment, and the values of parameters employed (in addition to those reported in *Tables 3, 7, 14, 21, 28* and *35*) are presented in *Table 41*. The analysis of the budgetary impact of GH treatment is estimated in *Table 42* (estimates of current treatment, prevalence and incidence are sourced in appendix 1).

The analysis of the budgetary impact is based on the prevalence for patients aged 8–15 years

TABLE 41 *Values of baseline parameters used to assess budgetary impact*

Parameter	GHD	TS	CRF	PWS	ISS
GH dose (mg/kg/week)	0.23	0.375	0.35	0.23	0.33
Length of GH treatment (years)	8	7	5	8	5
% of patients offered GH treatment after diagnosis	100%	100%	100%	100%	100%
% of diagnosed patients that accepted treatment	100%	95%	80%	90%	90%
Drop-out rate after first year of GH treatment	9.3%	17%	16%	0%	29%
Drop-out rate from growth monitoring after first year of monitoring	0%	41%	28%	0%	30%
Incremental cost of GH treatment	£69,872	£76,855	£72,273	£69,263	£69,573

TABLE 42 *Estimates of present-value total costs of GH treatment in England and Wales (base year 2000)*

Condition	Total cost of currently treated levels (A)	Total cost of treating prevalent levels of patients aged 8–15 years* (B)	Total cost of treating prevalent levels minus current treatment levels (B–A)	Total cost of incidence level
GHD	£81,533,030	£84,808,075	£3,275,045	£8,155,494
TS	£30,099,259	£68,368,882	£38,269,622	£8,546,110
CRF	£4,054,286	£11,177,275	£7,122,990	£3,163,708
PWS	£0	£15,290,605	£15,290,605	£1,911,326
ISS	£19,366,518	£724,576,738	£705,210,219	£89,327,595
All conditions	£135,053,093	£904,221,575	£769,168,482	£111,104,233

* *Costs relate to proportion of patients diagnosed and treated, and base case assumptions for offering and accepting treatment*

reported in *Table 2*. This seems a reasonable approach, with the age of 8 years being the earliest average age for the start of GH treatment in 1998;[8] however, other ways of analysing the budgetary impact can be considered (e.g. different average ages for the start of GH treatment). Using estimates of current treatment levels, the present values of total treatment costs for each condition in England and Wales are calculated. Prevalence estimates are used to estimate the present value of total treatment costs for all those children in need of treatment (the value is adjusted for diagnosis and assumes a proportion of children refuse treatment). The shortfall between the cost of treating current numbers of patients and the prevalence is an estimate of the maximum budgetary impact of the NHS extending treatment to patients with these conditions. Incidence data are used to estimate the annual budgetary impact of new cases.

Implications for parents and other caregivers

Particularly with younger children, parents play an important role in administering GH. Most treatment protocols require injections 6–7 times per week. It is not a trivial commitment by parents to see that these injections are given, and for some parents the stress of injecting their child may be considerable, at least initially. Even when children are able to inject themselves, parents maintain an important role in achieving good compliance.

Parents also assume an important role in helping children to understand what condition is being treated with GH and why they are being treated. The parents need to help children establish realistic goals for treatment and to understand why they are being treated, without labelling short stature as a disease.

Ethical issues

Unlike early treatment with GH, which depended upon limited supplies of GH derived from cadaveric pituitaries, supplies of recombinant GH are limited only by purchasers' willingness to pay. In this climate in which supplies are unlimited, but financial resources are not unlimited and clinical need may be difficult to judge, treatment decisions sometimes will be difficult. The current report has focused upon whether GH is effective and safe within certain conditions, but there is also debate about whether GH should be used to make some children taller and, if so, which children.[81,82] For instance, should GH be used only to treat disease *per se*, or might it be used to treat undesirable conditions? The resolution of the debate will depend, not only upon issues of treatment effectiveness and cost-effectiveness, but also upon the precision of diagnostic tests, the ability to predict treatment success, and the psychological effects of height and height changes – all of which need further research. It has also been suggested that alternatives to treating shortness with GH should be considered, such as psychological interventions. Many of these issues might be addressed by a greater focus on the assessment of quality of life in well-designed GH trials, rather than the narrow focus on growth that has dominated trials up to the present.

Factors relevant to NHS policy

The cost-effectiveness models are based on the *BNF* prices of recombinant human GH. In practice, local NHS payers may negotiate a lower actual price. There were no reliable data on actual prices paid to inform the analysis.

Mechanisms for funding GH prescriptions seem to vary considerably among health authorities. Therefore, uniform policy on prescribing GH would help to alleviate regional differences in prescribing.

In addition, clear policy will help to assure equitable treatment of all persons. TS occurs only in women, and CRF is more common in persons of African or Asian descent.

Chapter 13

Discussion

Statement of principal findings

GH in GHD

Although there was only one RCT that tested GH in patients with GHD, the use of GH is well established in this group. In these children, there is a demonstrated reduction of this fundamental hormone (albeit measured using tests that are somewhat arbitrary). GH treatment is therefore replacement therapy. Because most paediatricians would consider it unethical to withhold treatment, RCTs comparing GH with placebo are unrealistic, and the best available evidence for the effect of GH on final height comes from retrospective single-cohort studies.

Evidence shows that GH promotes both short-term growth and final height in these children with GHD. The summarised results suggest that HtSDS can be improved by approximately 1 SD with 1 year of treatment. Final height seems to be increased by approximately 1.3–1.6 SD (about 8.5–10.5 cm in boys and 7.5–9.5 cm in girls). The final height SDs correspond to average final heights of approximately 168 cm for boys and 155 cm for girls. These heights are within the normal range (i.e. within 2 SD of the normal mean). The best available method to estimate the effects of GH in this group of patients is still likely to underestimate the true effects. In addition, the included results from children, many of whom started treatment relatively late in childhood and/or with non-optimal doses or injection frequencies, may also underestimate the effects of GH in GHD.

The incremental cost-effectiveness estimate of GH treatment in GHD is about £6000 per centimetre gained in final height, which may be an over-estimate for the reasons mentioned previously. In addition to the effectiveness estimate, the ICER value is sensitive to the length of treatment and to an earlier age of the start of treatment. Both factors increase the cost of treatment. Further evidence, not yet available, on the impact of an earlier start of GH treatment on incremental final height is necessary to strengthen the validity of the cost-effectiveness analysis. The use of larger doses of GH during puberty increases the cost of treatment, but the evidence is lacking on how this practice impacts on final height.

GH in TS

RCT evidence shows that GH promotes both short-term growth and final height in girls with TS.

Short-term results suggest that GV may be enhanced by approximately 2.8 cm over the first year of GH treatment in these girls.

Final height of girls with TS has been assessed in only one RCT, which is available only in abstract form. These results suggest that the final height is approximately 146 cm in GH-treated girls, who are approximately 5 cm taller than untreated girls. This final height of treated girls with TS is still outside the normal range (i.e. more than 2 SD below the normal mean).

The currently summarised results demonstrate that GH can improve growth and final height in girls with TS. However, response to GH treatment in individual girls is quite variable.

The cost-effectiveness analysis estimated an ICER between £15,997 and £17,429 per centimetre gained in final height, but was found to be sensitive to the age at the start of GH treatment and the uncertainty in the estimated beneficial impact on the final height.

GH in CRF

RCTs and studies with non-randomised control groups show that GH promotes both short-term growth and final height in children with CRF.

Short-term trials demonstrate that GH given to children with CRF either prior to or after transplant increases growth. These effects appear to be in the range of approximately 0.8 SD over 1 year and 1.3 SD over 2 years.

The effect of GH on final height is difficult to assess because no RCTs that included an untreated group have been conducted to final height. The results available suggest that GH effects in improving height may be in the range of 3–9 cm in boys and 4–8 cm in girls, corresponding to final heights of approximately 162–165 cm in

boys and 151–156 cm in girls. These heights are at the lower bound of the normal range (i.e. approximately 2 SD below the normal mean).

The ICER result for GH treatment in CRF varies between £7403 and £24,093 per centimetre gained in final height and was based on two studies providing final height estimates. The study that demonstrates more beneficial impact of GH treatment reported median final heights, and the economic analysis is based on these estimates, which could be inaccurate if the incremental median final height differs from the incremental mean final height. The ICER results are sensitive to the length of treatment and drug dose employed. An earlier start of treatment and larger GH doses will increase the cost of treatment, and once again additional evidence on the impact on final height is needed to discuss the potential added benefits.

GH in PWS

Evidence from RCTs and a single-cohort study shows that GH promotes short-term growth, improved body composition and improved final height in PWS.

Short-term trials reported HtSDS approximately 1 SD greater in treated compared with untreated children. Treated children also had approximately 7–8% less fat and approximately 4 kg more lean body mass than untreated children. Children treated with GH did not differ from untreated children on a range of behaviours and psychological symptoms. However, within-group comparisons of children before and after GH treatment showed small improvements in obsession and skin-picking. GH treatment did not result in behavioural deterioration.

One small study of 16 treated children with PWS reported final height of 170 cm in boys and 159 cm in girls. These final heights are well within the normal range. This study did not include a control group, therefore the estimate of the effect of GH on final height should be interpreted with caution. In addition, it is not clear whether this small group of treated children was representative of other children with PWS. If it is assumed that the change in HtSDS from the inception of treatment to the end of treatment is a good estimate of treatment effect, then GH seems to improve final height by approximately 11 cm in males and 10 cm in females.

The cost-effectiveness results for PWS patients are difficult to interpret. The best-quality effectiveness evidence is related to an intermediate outcome measure, HtSDS at 1 year. If an assumption is made that the HtSDS at the end of treatment equals HtSDS at 1 year, the cost of GH treatment of PWS children is between £40,815 and £85,368 for about a unit increase in HtSDS. This estimate is sensitive to length of treatment and drug dose used.

The only study reporting final height in children with PWS (who also had GHD) provided an estimate of the gain in final height based upon the assumption that untreated children would remain at the pretreatment SD at final height. The incremental cost of each centimetre gained in final height based on this study is £7030. This result is highly sensitive to the effectiveness estimate.

GH in ISS

RCTs and studies with a non-randomised control group show that GH promotes both short-term growth and small gains in final height in children with ISS.

Studies suggest that short-term height gains can range from none to approximately 0.7 SD over 1 year.

Final height gains reported from non-randomised studies were approximately 2.5–7.5 cm, resulting in final heights of approximately 164 cm in boys and 155 cm in girls. These heights are near the lower bound of the normal range (i.e. approximately 2 SD below the normal mean).

The ICER for GH treatment of ISS children is based on two effectiveness studies and ranges from £13,498 to £27,202 per centimetre of final height increase. The impact of treatment on final height is the most important factor in the cost-effectiveness of GH treatment. Other important factors are the length of treatment and the drug dose employed.

General discussion

Although GH does promote short-term growth and increased final height, in many cases these gains are relatively small. Children who may be taller than they would otherwise have been may nonetheless be quite short relative to their peers. Growth and final height are dependent, not only upon hormonal factors, but also on the genetic endowment from parents, which should be considered when establishing realistic

expectations about the potential effects of GH on final height.

It should be noted that a concentration on height outcomes is likely to be biased toward finding positive effects of GH treatment. A wide range of other possible outcomes could be considered, although many of these would not be salient to the children or parents (e.g. physiological measures) or would be difficult to assess in children (e.g. quality of life). Most of these outcomes are not well represented in the literature but could perhaps be assessed in future research (see *Implications for research* on page 67).

It was beyond the scope of this review to consider the psychological effects on children of being short, outside the context of studies that would meet the criteria for inclusion for evaluation of GH effectiveness. Although three trials considering psychological outcomes have been included, none specifically assessed the effects of height on children's quality of life. The results reported by Rovet and Holland[13] do indirectly suggest that improved growth has positive effects on the self-concept and social functioning of girls with TS. However, many studies have produced variable results as to whether children are adversely affected by being short. Most concur that short-ness alone does not necessarily result in negative psychological consequences. Many studies have found no relation between the degree of shortness and psychological problems. It will be difficult to assess the psychological impact of GH treatment in children who have a complex variety of problems associated with their conditions, as is the case in GHD, TS, CRF or PWS.

Of even greater complexity but perhaps more importance is the consideration of whether shortness is a greater impediment to a healthy childhood than other physical or psychological factors that might be addressed within the same fiscal constraints. It is also important to bear in mind that, although it may be of considerable value to increase the height of children who may be dramatically shorter than their peers, there will always be children who make up the lowest percentiles on the height distribution curve.

It is clear that the costs of the drug therapy are the major costs that drive the cost of GH treatment for all five conditions. Costs rise in relation to the length of treatment (comparison of base cases 1 and 2 and case scenario A within conditions). Although case scenario A assumptions are based on evidence from clinical studies, in practice it is more likely that treatment starts at a younger age. This is reflected in the higher costs under assumptions of longer treatment duration. In general, the costs of growth monitoring are not substantial.

As seen by the wide range in minimum and maximum estimates of uncertainty, the impact of uncertainty surrounding key parameters in the model was clearly important. Full details of one- and two-way sensitivity analyses are presented in appendix 10. The two most important parameters for all conditions were the values attached to drug dose, length of treatment and effect size. The minimum and maximum ICER estimates need careful interpretation because the parameter values incorporated were values not necessarily achievable in practice.

The issue of treatment compliance should also be noted. GH treatment generally requires taking injections 6–7 times per week for several years. If patients do not adhere closely to the treatment regimen, effectiveness could be compromised. Compliance will also affect costs and cost-effectiveness. A systematic review of compliance was not within the scope of this review. Some sources indicate that compliance is relatively good. However, these reports are generally based on surveys and are therefore subject to various forms of reporting bias. A Scottish study[83] that investigated encashed prescriptions showed that approximately one-third of children were receiving less than 80% of their correct dose (i.e. they took GH < 292 days/year). In addition, there was a positive association between adherence and changes in HtSDS. However, there is no strong evidence to suggest that compliance in a trial setting for this long-term treatment would be significantly different than outside of a trial.

Adverse effects

Very few adverse events were reported in the context of the reported studies. However, some adverse effects may be very serious, such as diabetes mellitus. Extra care should be taken in monitoring for adverse effects such as diabetes mellitus, particularly in children whose condition may predispose them. The possibility that GH may affect glucose metabolism and be related to type 2 diabetes mellitus, both in children who may be predisposed as well as in others, requires additional research follow-up.

Most information about the safety of GH comes from large databases, which suggest that serious

adverse events are rare within the licensed indications. However, because some of the conditions in which GH is used may also predispose children to other serious conditions, monitoring should be rigorous.

Strengths and limitations of the review

This systematic review has certain strengths, including the following.

- It is independent of any vested interest.
- It brings together the evidence for the effectiveness of GH treatment for GHD, TS, CRF, PWS and ISS, and an economic evaluation, applying consistent methods of critical appraisal and presentation.
- It was guided by accepted principles for undertaking a systematic review. The methods of the review were set out in advance in a research protocol (appendix 2), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.
- To the extent possible, the review of clinical effectiveness relied upon evidence from RCTs. When this evidence was not available, the best evidence available was sought.
- The developed cost models take the NHS and social services' perspective, and estimate the full treatment costs depending on the main treatment parameters. These estimates, combined with the best evidence on the final height impact, informed the cost-effectiveness analysis.

In contrast, there were certain limitations placed upon the review.

- Due to differences in the design, duration and reporting of studies, as well as due to time restrictions, synthesis of the included studies was through narrative review with no formal meta-analysis.
- Lack of time also made it impossible to contact authors of studies to clarify details of the studies.
- The quality of the RCTs was assessed using the Jadad scale. Although the Jadad scale includes key elements by which to assess the quality of RCTs, including randomisation, blinding and withdrawals/drop-outs, it could be criticised for excluding other elements that may cause bias (e.g. not including the level of withdrawal/drop-out). It has also been pointed out that the Jadad scale "gives more weight to the quality of reporting than to actual methodological quality".[84]
- It should be noted that many of the conditions for which GH may be prescribed can be diagnosed at an early age. Therefore, GH might be prescribed for a relatively long time (e.g. 10–12 years or more). The duration of the vast majority of the studies reviewed was far shorter. Therefore, it is impossible to assess the true effects of GH in the context in which it may ultimately be prescribed. Even studies that considered final height generally involved prescribing GH for approximately 5–8 years. These studies may underestimate the impact on final height of GH treatment for a longer period. In addition, however, the costs of longer treatment would also be far greater.
- Given natural variations in GV, it has been considered that final height is the best indicator of the effectiveness of GH in promoting growth. However, the available evidence on final height is extremely limited. No studies that used the best methodology of double-blind placebo control have been conducted to final height in any of the conditions. Only one randomised trial including a no-treatment group in TS has been partially reported, and a second RCT reported near final height in ISS. Therefore, conclusions about the effects of GH on final height are tenuous.
- In two conditions (GHD and PWS), the effects of GH on final height were estimated by assuming that changes in HtSDS from the beginning of treatment to the final height represented the effects of GH treatment. The change in HtSDS was then converted to centimetres by referring to adult height norms. The initial assumption that treatment effects can be estimated by changes in HtSDS may be questionable, and the conversion to centimetres is approximate.
- In the light of the difficulty of interpreting quality-of-life evidence from the economic perspective, the economic evaluation analysis was limited to the cost-effectiveness analysis.

Other issues

The diagnosis of GHD must take into account clinical, auxological, biochemical and radiological data. Diagnosis is usually straightforward for severe GHD, but it is recognised that the diagnosis of moderate GHD can be difficult. Peak GH concentration below 10 µg/l, in response to two GH provocation tests, is traditionally the cut-off for

GHD. However, this value will vary depending on the assay used, and there is a lack of standardisation between centres.

This issue could be particularly relevant if GH is prescribed to children who are diagnosed with GHD, but not to those who are diagnosed with ISS. How to draw the diagnostic line may be a difficult decision if parents of children with ISS feel that their children are being unfairly denied treatment on the basis of arbitrary diagnostic criteria.

Implications for research

RCTs are required that focus on clear outcomes such as final height, rather than outcomes with poorly predictive surrogate markers (e.g. predicted adult height or target height).[85] These trials should be analysed on an intent-to-treat basis. Such trials should also compare different treatment regimens to assess which factors contribute most critically to benefit for the patient. Outstanding issues cannot be adequately addressed by non-experimental studies. Trials will need to be large, multicentre efforts and will require oversight from a coordinating body. Such trials require several years to conduct.

In GHD, it is considered unethical to withhold treatment from some children, as would be required to conduct an RCT of basic effectiveness. In the case of GHD, the best available methods should be used to minimise inaccuracies in estimating treatment effects. All such methods will be subject to some bias due to the use of surrogate outcomes or the use of old historical controls.

In addition to GH effects on height, more research should address quality of life in children who are treated. These studies should focus particularly on measures that can be used in economic modelling. Outstanding issues to be addressed in future research include:

- age of onset of treatment (usually regarded as the earlier the better)
- optimal dose of GH (usually regarded as larger dose for longer duration)
- age of onset of sex steroid therapy in TS (later and until growth is nearly complete so as not to increase bone age) and general puberty issues (also relevant to GHD)
- psychological issues
- heterogeneity of participants in studies (which could be masking a subset of those who could benefit long term)
- impact of GH treatment on QALYs during treatment and after final height is achieved (age and sex related)
- issues related to improving compliance and continuance with GH treatment.

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References

1. Preece MA. Disorders of growth. In: Ledingham JGG, Warrell DA, editors. Concise Oxford textbook of medicine. Oxford: Oxford University Press; 2000. p. 893–6.
2. Wit JM, Kamp GA, Rikken B. Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. *Pediatr Res* 1996;**39**:295–302.
3. Goh D, Evans JHC, Houston IB, Mallick NP, Morton MJS, Johnson RWG, *et al.* The changing pattern of children's dialysis and transplantation over 20 years. *Clin Nephrol* 1994;**42**:227–31.
4. Schaefer F, Wingen AM, Hennicke M, Rigden S, Mehls O. Growth charts for prepubertal children with chronic renal failure due to congenital renal disorders. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *Pediatr Nephrol* 1996;**10**:288–93.
5. Hauffa BP. One-year results of growth hormone treatment of short stature in Prader–Willi syndrome. *Acta Paediatr Suppl* 1997;**423**:63–5.
6. Price DA. Spontaneous adult height in patients with idiopathic short stature. *Horm Res* 1996; **45**(Suppl 2):59–63.
7. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. *Arch Dis Child* 1985;**60**:932–5.
8. Hilken J. UK audit of childhood growth hormone prescription, 1998. *Arch Dis Child* 2001;**84**:387–9.
9. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD guidelines for those carrying out or commissioning reviews. NHS CRD Report 4. York: NHS CRD; 1999.
10. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
11. Spitzer WO, Lawrence V, Dales R, Hill G, Archer MC, Clarck P, *et al.* Links between passive smoking and disease; a best-evidence synthesis. *Clin Invest Med* 1990;**13**:17–42.
12. Anthony D, Stevens A. Growth hormone in children. Development and Evaluation Committee Report No. 57. Bristol: NHS Executive South West; 1996.
13. Rovet J, Holland J. Psychological aspects of the Canadian randomized controlled trial of human growth hormone and low-dose ethinyl estradiol in children with Turner syndrome. *Horm Res* 1993;**39**:60–4.
14. Singh J, Cuttler L, Shin M, Silvers JB, Neuhauser D. Medical decision-making and the patient: understanding preference patterns for growth hormone therapy using conjoint analysis. *Med Care* 1998; **36**(8 Suppl):AS31–45.
15. Teeling-Smith G, West R. Economic evaluation of growth hormone therapy. *OHE Briefing* 1991; No. 28.
16. British Society for Paediatric Endocrinology and Diabetes. Consensus statement on the diagnosis of growth hormone deficiency. 2001. URL: http://www.bsped.org.uk/NICEGHD.html
17. UK Child Growth Foundation. Boys four-in-one growth charts. London: Child Growth Foundation; 1996.
18. UK Child Growth Foundation. Girls growth chart (birth–18 years), UK cross-sectional reference data: 1996. London: Child Growth Foundation; 1996.
19. British National Formulary. No. 41. London: British Medical Association and Royal Pharmaceutical Society; 2001 [accessed 2001 May]. URL: http://www.bnf.org/
20. Netten A, Dennet J, Knight J. Unit costs of health and social care 1999. Canterbury: Personal Social Services Research Unit, University of Kent; 1999.
21. Contracting Unit, Southampton University Hospitals Trust. 2001 [unpublished dataset].
22. NICE. Technical guidance for manufacturers and sponsors on making a submission to a technology appraisal. 2001. URL: http://www.nice.org.uk
23. Soliman AT, Abdul-Khadir MM. Growth parameters and predictors of growth in short children with and without growth hormone (GH) deficiency treated with human GH: a randomized controlled study. *J Trop Pediatr* 1996;**42**:281–6.
24. Canadian Growth Hormone Advisory Committee. Growth hormone treatment to final height in Turner syndrome: a randomized controlled trial. *Horm Res* 1998;**50**(Suppl 3):25.
25. Rosenfeld RG. Non-conventional growth hormone therapy in Turner syndrome: the United States experience. *Horm Res* 1990;**33**:137–40.

26. Rosenfeld RG. Acceleration of growth in Turner syndrome patients treated with growth hormone: summary of three-year results. *J Endocrinol Invest* 1989;**12**(8 Suppl 3):49–51.

27. Ross JL, Feuillan P, Kushner H, Roeltgen D, Cutler GB Jr. Absence of growth hormone effects on cognitive function in girls with Turner syndrome. *J Clin Endocrinol Metab* 1997;**82**:1814–17.

28. Fine RN, Kohaut EC, Brown D, Perlman AJ. Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. *J Pediatr* 1994;**124**:374–82.

29. Powell DR, Liu F, Baker BK, Hintz RL, Lee PDK, Durham SK, *et al.* Modulation of growth factors by growth hormone in children with chronic renal failure. *Kidney Int* 1997;**51**:1970–9.

30. Hokken-Koelega ACS, Stijnen T, de Muinck Keizer-Schrama SMPF, Wit JM, Wolff ED, de Jong MCJW, *et al.* Placebo-controlled, double-blind, cross-over trial of growth hormone treatment in prepubertal children with chronic renal failure. *Lancet* 1991;**338**:585–90.

31. Broyer M. Results and side-effects of treating children with growth hormone after kidney transplantation – a preliminary report. Pharmacia & Upjohn Study Group. *Acta Paediatr Suppl* 1996;**417**:76–9.

32. Hokken-Koelega AC, Stijnen T, de Jong RC, Donckerwolcke RA, Groothoff JW, Wolff ED, *et al.* A placebo-controlled, double-blind trial of growth hormone treatment in prepubertal children after renal transplant. *Kidney Int Suppl* 1996;**53**:S128–34.

33. Carrel AL, Myers SE, Whitman BY, Allen DB. Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader–Willi syndrome: a controlled study. *J Pediatr* 1999;**134**:215–21.

34. Lindgren AC, Hagenas L, Muller J, Blichfeldt S, Rosenborg M, Brismar T, *et al.* Effects of growth hormone treatment on growth and body composition in Prader–Willi syndrome: a preliminary report. The Swedish National Growth Hormone Advisory Group. *Acta Paediatr Suppl* 1997;**423**:60–2.

35. Lindgren AC, Hagenas L, Muller J, Blichfeldt S, Rosenborg M, Brismar T, *et al.* Growth hormone treatment of children with Prader–Willi syndrome affects linear growth and body composition favourably. *Acta Paediatr* 1998;**87**:28–31.

36. Whitman BY, Myers S, Carrel A, Allen D. A treatment/control group study of growth hormone treatment: impact on behavior – a preliminary look. *Endocrinologist* 2000;**10**(4 Suppl 1):31S–7S.

37. McCaughey ES, Mulligan J, Voss LD, Betts PR. Randomised trial of growth hormone in short normal girls. *Lancet* 1998;**351**:940–4.

38. Idiopathic short stature: results of a one-year controlled study of human growth hormone treatment. Genentech Collaborative Study Group. *J Pediatr* 1989;**115**:713–19.

39. McCaughey ES, Mulligan J, Voss LD, Betts PR. Growth and metabolic consequences of growth hormone treatment in prepubertal short normal children. *Arch Dis Child* 1994;**71**:201–6.

40. Barton JS, Gardiner HM, Cullen S, Hindmarsh PC, Brook CGD, Preece MA. The growth and cardiovascular effects of high-dose growth hormone therapy in idiopathic short stature. *Clin Endocrinol* 1995;**42**:619–26.

41. Volta C, Bernasconi S, Tondi P, Salvioli V, Ghizzoni L, Baldini A, *et al.* Combined treatment with growth hormone and luteinizing hormone releasing hormone–analogue (LHRHa) of pubertal children with familial short stature. *J Endocrinol Invest* 1993;**16**:763–7.

42. Cowell CT. Effects of growth hormone in short, slowly growing children without growth hormone deficiency. Australasian Paediatric Endocrine Group. *Acta Paediatr Scand Suppl* 1990;**366**:29–30.

43. Ackland FM, Jones J, Buckler JM, Dunger DB, Rayner PH, Preece MA. Growth hormone treatment in non-growth hormone-deficient children: effects of stopping treatment. *Acta Paediatr Scand Suppl* 1990;**366**:32–7.

44. Cutfield W, Lindberg A, Chatelain P, Ranke M, Wilton P. Final height in idiopathic growth hormone deficiency: the KIGS experience. *Acta Paediatr Suppl* 1999;**88**(Suppl 428):72–5.

45. August G, Julius J, Blethen S. Adult height in children with growth hormone deficiency. *Pediatrics* 1998;**102**:512–16.

46. Dacou-Voutetakis C, Karavanaki-Karanassiou K, Petrou V, Georgopoulos N, Maniati-Christidi M, Mavrou A. The growth pattern and final height of girls with Turner syndrome with and without human growth hormone treatment. *Pediatrics* 1998;**101**(4 Pt 1):663–8.

47. Hochberg Z, Zadik Z. Final height in young women with Turner syndrome after GH therapy: an open controlled study. *Eur J Endocrinol* 1999;**141**:218–24.

48. Pasquino AM, Passeri F, Municchi G, Segni M, Pucarelli I, Larizza D, *et al.* Final height in Turner syndrome patients treated with growth hormone. *Horm Res* 1996;**46**:269–72.

49. Taback SP, Collu R, Deal CL, Guyda HJ, Salisbury S, Dean HJ, *et al.* Does growth-hormone supplementation affect adult height in Turner's syndrome? *Lancet* 1996;**348**:25–7.

50. Haffner D, Schaefer F, Nissel R, Wuhl E, Tonshoff B, Mehls O. Effect of growth hormone treatment on the adult height of children with chronic renal failure. *N Engl J Med* 2000;**343**:923–30.

51. Janssen F, Van Damme LR, Van Dyck M, Hall M, Schurmans T, Herman J, *et al.* Impact of growth hormone treatment on a Belgian population of short children with renal allografts. *Pediatr Transplant* 1997;**1**:190–6.

52. Angulo MA, Castro-Magana MS, Canas JA, Arguello R, Lamerson M, Tapiador C, *et al.* Final height in Prader–Willi syndrome (PWS) children treated with recombinant growth hormone (rhGH). *Pediatr Res* 2000;**47**:1400.

53. Zadik Z, Mira U, Landau H. Final height after growth hormone therapy in peripubertal boys with a subnormal integrated concentration of growth hormone. *Horm Res* 1992;**37**:150–5.

54. Hindmarsh PC, Brook CGD. Final height of short normal children treated with growth hormone. *Lancet* 1996;**348**:13–16.

55. Juul A, Bernasconi S, Chatelain P, Hindmarsh P, Hochberg Z, Hokken KA, *et al.* Diagnosis of growth hormone (GH) deficiency and the use of GH in children with growth disorders. *Horm Res* 1999;**51**:284–99.

56. Preece MA. Normal growth and its disorders. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. Oxford textbook of medicine. Oxford: Oxford University Press; 1996. p. 1695–700.

57. Guyda H. Four decades of growth hormone therapy for short children: what have we achieved? *J Clin Endocrinol Metab* 1999;**84**:4307–16.

58. Hailey JA, Bath LE, Kelnar CJH. Idiopathic short stature – diagnostic and therapeutic dilemmas. *J R Soc Med* 1999;**14**:61–5.

59. Saenger P. Turner's syndrome. *N Engl J Med* 1996;**335**:1749–54.

60. Ranke MB, Stubbe P, Majewski F, Bierich JR. Spontaneous growth in Turner's syndrome. *Acta Paediatr Scand Suppl* 1988;**343**:22–30.

61. Gault EJ, Donaldson MDC. Efficacy of growth hormone therapy in Turner's syndrome. 2001. URL: http://www.bsped.org.uk/XONICE.html

62. Rochiccioli P, David M, Malpuech G, Colle M, Limal JM, Battin J, *et al.* Study of final height in Turner's syndrome: ethnic and genetic influences. *Acta Paediatr* 1994;**83**:305–8.

63. Betts PR, Butler GE, Donaldson MD, Dunger DB, Johnston DI, Kelnar CJ, *et al.* A decade of growth hormone treatment in girls with Turner syndrome in the UK. UK KIGS Executive Group. *Arch Dis Child* 1999;**80**:221–5.

64. Gharib H, Saenger P, Zimmerman D. AACE clinical practice guidelines for growth hormone use in adults and children. *Endocr Pract* 1998;**4**:165–73.

65. Gusmano R, Perfumo F. Worldwide demographic aspects of chronic renal failure in children. *Kidney Int Suppl* 1993;**41**:S31–5.

66. Saborio P, Hahn S, Hisano S, Latta K, Scheinman JI, Chan JCM. Chronic renal failure: an overview from a pediatric perspective. *Nephron* 1998;**80**:134–48.

67. Vimalachandra D, Craig JC, Cowell C, Knight JF. Growth hormone treatment for chronic renal failure in children [protocol]. *The Cochrane Library* 2001;(2).

68. UK Renal Registry. 2nd Annual Report of the Paediatric Renal Registry 1999 [accessed 2001 Jan]. URL: http://www.renalreg.com/report99/

69. Considerations related to the use of recombinant human growth hormone in children. American Academy of Pediatrics Committee on Drugs and Committee on Bioethics. *Pediatrics* 1997;**99**:122–9.

70. Lindgren AC, Ritzen EM. Five years of growth hormone treatment in children with Prader–Willi syndrome. Swedish National Growth Hormone Advisory Group. *Acta Paediatr Suppl* 1999; **88**(Suppl 433):109–11.

71. Ranke MB. Towards a consensus on the definition of idiopathic short stature. *Horm Res* 1996; **45**(Suppl 2):64–6.

72. Blethen SL, Allen DB, Graves D, August G, Moshang T, Rosenfeld R. Safety of recombinant deoxyribonucleic acid-derived growth hormone: the National Cooperative Growth Study experience. *J Clin Endocrinol Metab* 1996;**81**:1704–10.

73. Frisch H. Pharmacovigilance: the use of KIGS (Pharmacia and Upjohn International Growth Database) to monitor the safety of growth hormone treatment in children. *Endocrinol Metab Suppl* 1997;**4**(Suppl B):83–6.

74. Cutfield WS, Wilton P, Bennmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, *et al.* Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* 2000;**355**:610–13.

75. Blethen SL, MacGillivray MH. A risk–benefit assessment of growth hormone use in children. *Drug Saf* 1997;**17**:303–16.

76. Growth Hormone Research Society. Consensus critical evaluation of the safety of recombinant human growth hormone administration: statement from the Growth Hormone Research Society. *J Clin Endocrinol Metab* 2001;**86**:1868–70.

77. Schaefer F, Haffner D, Wuhl E, Mehls O. Long-term experience with growth hormone treatment in children with chronic renal failure. *Perit Dial Int* 1999;**19**(Suppl 2):S467–72.

78. Lindgren AC. Side-effects of growth treatment in Prader–Willi syndrome. *Endocrinologist* 2000; **10**(4 Suppl 1):63S–4S.

79. Kirk J. BSPED consensus guidelines: use of growth hormone in non-licensed indications. 2001. URL: http://www.bsped.org.uk/ULNICE.html

80. Guidelines for the use of growth hormone in children with short stature. A report by the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. *J Pediatr* 1995;**127**:857–67.

81. Lantos JD. Growth hormone and short stature: constructing a disease and constructing a market for treatment. *Forum Trends Exp Clin Med* 1997;**7**:288–93.

82. Kelnar CJH, Albertsson-Wikland K, Hintz RL, Ranke MB, Rosenfeld RG. Should we treat children with idiopathic short stature? *Horm Res* 1999;**52**:150–7.

83. Hunter I, de Vries C, Morris A, MacDonald T, Greene S. Human growth hormone therapy: poor adherence equals poor growth. *Arch Dis Child* 2000;**82**(Suppl 1):28.

84. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282**:1054–60.

85. Kelnar CJ. Cost–benefit analysis is the key. *Arch Dis Child* 2000;**83**:176–7.

86. Office for National Statistics. Births: 1998, UK [accessed 2001 Jan]. URL: http://www.statistics.gov.uk/statbase/xsdataset.asp

87. Office for National Statistics. Population: age and sex, 1971 onwards [accessed 2001 Jan]. URL: http://www.statistics.gov.uk/statbase/xsdataset.asp

88. UK Child Growth Foundation. Endocrine gland disorders. 2001. URL: http://www.exnet.com/staff/sys4/endr.html

89. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EH, Farquhar JW. Prevalence of severe growth hormone deficiency. *BMJ* 1977;**2**:427–30.

90. UK Child Growth Foundation. Turner syndrome. 2001. URL: http://www.exnet.com/staff/sys4/ts2.html

91. Prader–Willi Syndrome Association (UK). A to Z of Prader–Willi syndrome. 2001. URL: http://www.pwsa-uk.demon.co.uk/

92. Ranke MB, Grauer ML, Kistner K, Blum WF, Wollmann HA. Spontaneous adult height in idiopathic short stature. *Horm Res* 1995;**44**:152–7.

93. Finkelstein BS, Silvers JB, Marrero U, Neuhauser D, Cuttler L. Insurance coverage, physician recommendations, and access to emerging treatments. *JAMA* 1998;**279**:663–8.

94. UK Child Growth Foundation. Child growth. URL: http://www.eguidelines.co.uk

95. Taback SP, Guyda HJ, Van Vliet G. Pharmacological manipulation of height: qualitative review of study populations and designs. *Clin Invest Med* 1999;**22**:53–9.

96. Haeusler G, Frisch H. Methods for evaluation of growth in Turner's syndrome: critical approach and review of the literature. *Acta Paediatr* 1994;**83**:309–14.

97. Barnes N, Cheetham T. Short stature. *Prescr J* 1995;**35**:212–20.

98. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. *Health Technol Assess* 2001;**5**(4).

99. The EuroQoL Group. Homepage of EQ-5D. 2001. URL: http://www.euroqol.org/

100. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system: Health Utility Index Mark 2. *Med Care* 1996;**34**:702–22.

101. Boyle MH, Furlong WJ, Feeny DH, Torrance GW, Hatcher J. Reliability of the Health Utilities Index–Mark III used in the 1991 cycle 6 Canadian General Social Survey Health Questionnaire. *Qual Life Res* 1995;**4**:249–57.

102. Apajasalo M, Rautonen J, Holmberg C, Sinkkonen J, Aalberg V, Pihko H, *et al.* Quality of life in pre-adolescence: a 17-dimensional health-related measure (17D). *Qual Life Res* 1996;**5**:532–8.

103. Apajasalo M, Sintonen H, Holmberg C, Sinkkonen J, Aalberg V, Pihko H, *et al.* Quality of life in early adolescence: a sixteen-dimensional health-related measure (16D). *Qual Life Res* 1996;**5**:205–11.

104. Kaplan RM, Ganiats T, Sieber W, Anderson JP. The Quality of Well-being Scale. *Bull Med Outcome Trust* 1996;**4**(3):2–3.

105. Myers SE, Carrel AL, Whitman BY, Allen DB. Physical effects of growth hormone treatment in children with Prader–Willi syndrome. *Acta Paediatr Suppl* 1999;**88**(Suppl 433):112–14.

Appendix 1

Incidence, prevalence and current treatment patterns

Incidence and prevalence

Precise estimates for incidence and prevalence for the conditions of interest are sometimes difficult to obtain. The figures in *Table 2* are estimates from the best available evidence. However, because incidence and prevalence figures can sometimes vary widely within conditions, these figures should be considered as rough estimates.

Estimates that rely on birth rates are based on 1998 live births in the UK[86] (see *Table 43*).

TABLE 43 *Live births in the UK in 1998*

Number of live births	Male	Female	Total
England	308,663	293,448	602,111
Wales	17,053	16,385	33,438

Estimates that depend on population are based on 1999 estimates[87] for the population of children under 16 years of age in England and Wales (see *Table 44*).

TABLE 44 *Population of children under 16 years of age in the UK in 1999*

	Number of children < 16 years of age
England	10,097,000
Wales	597,000

GHD

Incidence

The UK Child Growth Foundation[88] estimates that idiopathic GHD affects approximately 1 in 5000 births in the UK population. Incidence figures were based on the birth statistics presented in *Table 43*. The incidence figures were based on idiopathic GHD and are therefore an underestimate because they do not include children who have acquired GHD from causes such as radiation treatment.

Prevalence

Prevalence was based on a survey conducted in three Scottish cites that reported the prevalence of severe GHD as 27 per 100,000.[89] Therefore, prevalence was estimated as 27 per 100,000 child population under 16 years of age in England and Wales. The prevalence figure would include children with GHD arising from any aetiology.

TS

Incidence

Incidence estimates for TS range from 1 in 1500 to 1 in 3500 live female births. The UK Child Growth Foundation estimates that TS occurs in approximately 1 in 2500 live female births.[90] Incidence figures were based upon the birth rates cited in *Table 43*, assuming TS occurs in 1 in 2500 female births.

Prevalence

It was assumed that there was no mortality. Therefore, incidence figures were multiplied by 16 to estimate the number of girls with TS between birth through 15 years of age.

CRF

Incidence

Incidence figures for CRF in children vary widely. Goh and co-workers[3] monitored referrals to renal replacement therapy in the North West Region of England between 1968 and 1988. Their incidence estimate for renal replacement therapy was 8.5 children per million of child population. Therefore, incidence was based on the child population figures noted in *Table 44*.

Prevalence

The prevalence figures were based on the UK Renal Registry,[68] which cites a prevalence figure for CRF of 12.2 per million total population. The resulting figures are also close to the actual number of paediatric patients in the registry across the UK and Ireland in 1998, which were 755 patients under age 18 years and 532 patients under age 15 years.

PWS

Incidence

The Prader–Willi Syndrome Association (UK)[91] estimates that PWS occurs in approximately 1 in 15,000 to 1 in 20,000 live births. Other estimates suggest that it occurs in 1 in 25,000 births. The cited incidence figure was the midpoint between an incidence of 1 in 15,000 and 1 in 25,000 live births.

Prevalence

It was assumed that there was no mortality within the first 15 years of life. Therefore, incidence figures were multiplied by 16 to estimate the number of children with PWS from birth through 15 years of age.

ISS

ISS is not a disease, and therefore specific diagnostic criteria cannot be used to determine who has ISS. ISS generally is defined by a combination of factors. There is variation in the definition of ISS and in final height for children who present as very short in childhood. Therefore, it is very difficult to estimate the number of children who might be given GH because they do not have a diagnosis such as the diagnoses above that are predictive of growth failure. The prevalence estimate is intended to indicate the number of short children who might be prescribed GH.

Prevalence

Most commonly, children who might be prescribed GH on the basis of ISS meet at least two criteria. First, children must be short (generally below the 3rd percentile of height). In addition, they must be growing slowly. Therefore, many fewer than the lowest 3% of children in height also have a low growth rate and might be prescribed GH.

It is difficult to estimate how many of the lowest 3% of children in height might actually be prescribed GH. One indication is the number of such children who end up as very short adults, although admittedly it may be difficult to determine who these children are when growth failure is first suspected in childhood. Ranke and co-workers[92] evaluated German children below the 3rd percentile for height and found that only 5% did not reach an adult height more than 2 SD below the mean. Therefore, we might expect that approximately 5% of very short children might be candidates for GH. Another way of evaluating which very short children might be prescribed GH would be to ask physicians for their opinions. In a survey study in the USA,[93] hypothetical profiles of short children (including height and growth information) were presented to primary care physicians and endocrinologists. Only 33% of these patients would have been referred to an endocrinologist, and of those 26% would have been recommended for GH treatment. Therefore, 9% of the short children might be referred for GH treatment. The prevalence estimate used these two suggestions for how many very short children might be prescribed GH. It was assumed that 3% of the population would be of very short stature and that between 5% and 9% (i.e. 7%) of those would be recommended for GH treatment.

Incidence

The incidence estimate was one-sixteenth of the prevalence.

Estimates of children currently treated

The estimates for the numbers of children being treated with GH were based upon a UK audit of GH prescriptions performed in 1998.[8] The reported figures are for prescriptions to children under 16 years of age.

The number of prescriptions issued to children with CRF was not broken down by country. The number of prescriptions in the UK was multiplied by 0.8855 (the England and Wales proportion of the total UK population) to estimate the number of prescriptions issued to children with CRF in England and Wales.

The number of prescriptions issued to children with ISS was not separately reported.[8] The cited figure is the number of 'all other' prescriptions for unlicensed indications in the UK (not including intrauterine growth retardation, Noonan syndrome and bony dysplasia) multiplied by 0.8855 (the England and Wales proportion of the total UK population).

Appendix 2

Review methods

The *a priori* methods described in the protocol for the review are included below. The protocol was sent for expert comments to members of the advisory group for the review (see *Acknowledgements*). Helpful comments were received relating to the general content of the research protocol, but there were none that identified specific problems with the methods of the review. Methods that were amended from the protocol are outlined in chapter 2.

Full title of research question

- The clinical effectiveness and cost-effectiveness of growth hormone in children.

Clarification of research question and scope

- The aim of the review is to provide a rapid and systematic review of the effectiveness and cost-effectiveness of growth hormone in children suffering from growth hormone deficiency (usually idiopathic), chronic renal failure, Turner syndrome, Prader–Willi syndrome and idiopathic short stature.
- Growth hormone deficiency, Turner syndrome, Prader–Willi syndrome and chronic renal failure are the licensed indications for treatment of children with growth hormone (somatropin) in the UK.
- The review will be from the perspective of the NHS and Personal Social Services regarding costs and will appraise the evidence on the benefits from the societal (children/parents/carers) perspective if available or from the perspective taken in the published study/ies.

Report methods

- The review will be a systematic review following the general principles outlined in NHS Centre for Reviews and Dissemination (CRD) Report 4.
- Meta-analyses, using the Cochrane Review Manager software, will be undertaken if appropriate.
- It should be noted that the research protocol will be updated as the research programme progresses. Any changes in the protocol will be notified to the NCCHTA and NICE.

Search strategy

- We will search the following electronic databases: Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluations Database (EED) and HTA database, MEDLINE (SilverPlatter®), PubMed (for the latest publications), EMBASE, National Research Register, Science Citation Index, BIOSIS, EconLit, Medical Research Council (MRC) Trials database, Early Warning System and Current Controlled Trials. These will be searched for the periods covered by the databases up until April 2001 and will be limited to the English language.
- Bibliographies of related papers will be assessed for relevant studies.
- Experts will be contacted for advice and peer review, and to identify additional published and unpublished references.
- Industry submissions to NICE will be searched for studies that meet the inclusion criteria. In addition, we will be seeking a list of trials from the industry via NICE at the start of the review, as a check on the completeness of ascertainment of our searches.

Inclusion and exclusion criteria

- The intervention is biosynthetic human growth hormone (somatropin), which is marketed by five companies in the UK: Pharmacia, Lilly, Novo Nordisk, Serono and Ferring. Respectively, the brand names of their somatropin are: Genotropin, Humatrope, Norditropin, Saizen and Zomacton. Each product has a sequence identical to that of human growth hormone.
- Participants are children suffering from one of five conditions: growth hormone deficiency, chronic renal failure, Turner syndrome, Prader–Willi syndrome and idiopathic short stature. Studies of intrauterine growth retardation will not be included.
- Outcomes will focus on those that are clinically relevant to children with growth deficiencies and growth failure. The gold-standard outcome measure of effectiveness of growth hormone

treatment is final height, but most studies are of insufficient duration to report this measure. Therefore short-term growth responses to treatment are assessed, such as height SDS and height velocity. Quality-of-life measures will also be reported where available.
- For each condition, we will include systematic reviews of RCTs, and individual RCTs, that assess the effects of growth hormone compared with placebo or no intervention on any of the above patient-relevant outcomes. If final height is not an outcome in one of the RCTs for that condition, searches will move down the hierarchy of evidence for other studies (controlled studies, case controlled studies, case series) reporting final height.
- We will identify and appraise economic evaluations of somatropin in children suffering from one of the five conditions. The inclusion criteria will be that studies must: be published; be available in full (i.e. excluding abstracts) to enable adequate quality assessment since, within the scope of this rapid review, it was not possible to contact authors for further details; include a comparator (or placebo); include both the costs and consequences (outcomes).
- Inclusion criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Quality assessment strategy

- The quality of included systematic reviews will be assessed using NHS CRD (University of York) six criteria,[9] RCTs will be judged using Jadad criteria,[10] and non-RCTs using modified Spitzer criteria[11] (see appendices 4 and 5).
- Quality of economic evaluations will be assessed for their internal validity (i.e. the methods used) using the *BMJ* checklist,[*] and external validity (i.e. the generalisability of the economic study to the population of interest) using a series of relevant questions.
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion.

Methods of analysis/synthesis

- The clinical effectiveness of human growth hormone in children will be synthesised through a narrative review with full tabulation of results of all included studies. We will consider carrying out meta-analyses using the Cochrane Review Manager software if that is considered practical and appropriate, in terms of heterogeneity and number of studies.
- The review will include a QUOROM-style flowchart of trials searched for and included in the review. This will include trials excluded, with reasons.
- Observations and insights on starting/stopping rules for treatment and optimal treatment strategies identified from the included clinical effectiveness studies will be reported.

Methods for estimating quality of life, costs and cost-effectiveness

- Cost-effectiveness will be assessed by a two-stage procedure. Firstly, a narrative review of published economic evaluation studies will be synthesised. The second stage will be to adapt an existing cost-effectiveness model or construct a new one using the best available evidence to determine cost-effectiveness in a UK setting.
- In order to determine applicability and resource implications to the NHS and Personal Social Services, resources and costs will be sought from published UK sources (e.g. *BNF* or published studies) and where appropriate and available, local NHS and Personal Social Services costs.
- Effectiveness data, in terms of the outcomes described in the above section will be extracted from published trials and used in association with the cost data to obtain measures of cost-effectiveness. If available, quality-of-life information will be obtained from the literature or other sources to calculate cost–utility estimates in terms of cost per QALY.
- The robustness of the results to the assumptions made in the model will be examined through sensitivity analysis and/or probabilistic sensitivity analysis.

[*] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. *BMJ* 1996;**313**:275–83.

Appendix 3

Sources of information, including databases searched and search terms

The following databases were searched for published studies, recently completed studies and ongoing research for the assessment of effectiveness.

Databases searched	Issue or dates searched	
	Effectiveness search	**Economics search**
Cochrane Library (Database of Systematic Reviews and Controlled Trials Register)	2001 Issue 1 Update: 2001 Issue 3	
MEDLINE (SilverPlatter)	2 Apr 2001 and 18 Apr 2001 Update: 25 Sep 2001	May 2001
DARE (NHS CRD, University of York)	25 Sep 2001	
NHS EED (NHS CRD, University of York)	24 Oct 2000 Update: 25 Sep 2001	May 2001
PubMed	25 Sep 2001	May 2001
EMBASE	5 Oct 2000 and 28 Apr 2001 Update: 25 Sep 2001	May 2001
Science Citation Index/ Social Sciences Citation Index	6 Oct 2000 Update: 25 Sep 2001	May 2001
BIOSIS	6 Oct 2000 Update: 25 Sep 2001	May 2001
EconLit	24 Oct 2000 Update: 26 Sep 2001	
PsycINFO	5 Oct 2000 Update: 25 Sep 2001	
Web of Science Proceedings	6 Oct 2000 Update: 26 Sep 2001	May 2001
Health Management Information Consortium	26 Sep 2001	May 2001
National Library of Medicine Gateway		May 2001
Searches for research in progress		
National Research Register	20 Oct 2000 Update: 25 Sep 2001	May 2001
The Cochrane Library	2001 Issue 1 Update: 2001 Issue 3	
ClinicalTrials.gov	28 Nov 2000 Update: 26 Sep 2001	
Current Controlled Trials	26 Sep 2001	
Early Warning System	26 Sept, 2001	

Primary search terms for effectiveness searches were:

- somatropin*, somatotropin*, somatotrophin*, growth, hormone, growth hormone, genotropin*, humatrope*, norditropin*, saizen*, zomacton*, nutropin
- growth hormone deficiency (meshtree), growth hormone deficien*, GH-deficien*, GHD
- kidney failure, chronic (mesh heading), chronic near (renal or kidney) near failure, CRF, chronic renal insufficiency, CRI
- Turner*, Turner syndrome (meshtree)
- Prader–Willi syndrome (mesh heading)

- idiopathic short stature, ISS, short, stature
- child, adoles*
- adult near height, final near height.

Bibliographies of related papers were assessed for relevant studies.

Experts were contacted for advice and peer review, and to identify additional published and unpublished references.

Industry submissions to NICE were searched for studies that met the inclusion criteria. In addition, a list of trials from the industry was sought via NICE at the start of the review, as a check on the completeness of ascertainment of our searches.

Searches for GH and economics

Primary search terms for economics searches were:

- Mesh trees: "Economics", "Costs-and-Cost-Analysis", "Economics-Dental", "Economics-Hospital", "Economics-Medical", "Economics-Nursing", "Economics-Pharmaceutical", "Fees-and-Charges", "Budgets"
- cost*, economic*, pharmacoeconomic*, price*, pricing, quality adjusted life year*, qaly*, willingness to pay, conjoint analys*, health measurement questionnaire, quality near life, ihql, wellbeing, well-being, qwb, health utilit* ind*, multiattribute* or multi attribute* or multi-attribute*, health ind*, utilit* analys*, classification near2 illness state*, 12d,15d, euroqol* or eq-5d or eq 5d or eq5d, rating scale*, visual analog*, persontradeoff or (person tradeoff) or (person trade off) or (person trade*), (health near2 stat*) or (health-status) or (health near2 utilit*), standard gamble*, timetradeoff or (time tradeoff) or (time trade off) or (time trade*).

Searches were restricted to English.

Full search strategies for both effectiveness and economics searches are available upon request.

Appendix 4

Quality assessment for RCTs (Jadad quality score)[10]

Questions to assess the likelihood of bias

Was the study described as randomised (this includes the use of words such as randomly, random and randomisation)?
Was the study described as double-blind?
Was there a description of withdrawals and drop-outs?

Scoring the items

Either give a score of 1 point for each 'yes' or 0 points for each 'no' There are no in-between marks.

Give 1 additional point if:

- for question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, etc.) and/or
- if for question 2, the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if:

- for question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) and/or
- for question 2, the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet vs injection with no double dummy).

Guidelines for assessment[10]

1. Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

2. Double-blinding

A study must be regarded as double-blind if the word 'double-blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Withdrawals and drop-outs

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Appendix 5

Quality assessment for non-RCTs

An assessment was used for included studies that were not RCTs. These quality criteria were adapted from Spitzer and co-workers.[11] The original checklist was modified to include items of particular relevance to assessing non-randomised studies.

1. Does the trial use proper random assignment?
   A study with proper random assignment would include multiple conditions with random assignment and would use an appropriate method for the assignment (e.g. table of random numbers, computer generated, etc.) with allocation concealment.
2. Did the study use proper sampling?
   A study with proper sampling would allow for all patients to be equally likely to enter the study (e.g. patients selected consecutively or randomly sampled).
3. Was the sample size adequate?
   Proper sample size enables adequately precise estimates of priority variables found to be significant (e.g. can compute CI within relatively small range or relatively small standard error of the mean).
4. Were the criteria for definition or measurement of outcomes objective or verifiable?
   Good outcome measures would be defined by clear methods for measuring outcomes (i.e. an operational definition) that are public, verifiable and repeatable.
5. Were outcomes measured with blind assessment?
   In studies with blind assessment, those individuals evaluating outcomes are unaware of the treatment status of those being evaluated.
6. Were objective criteria used for the eligibility of patients?
   Good eligibility criteria would use clear, public, verifiable characteristics that are applied for inclusion and exclusion.
7. Were attrition rates (%) provided?
   A study should report the number of patients who could not be contacted for outcome measures or later (e.g. drop-outs or withdrawals due to treatment toxicity).
8. Were groups under comparison comparable?
   Comparable groups show similar results across a reasonable range of baseline characteristics that could be expected to affect results.
9. Are the results generalisable?
   Generalisable results come from a sample population that is representative of the population to which results would be applied.

Appendix 6

Excluded studies

Assessment of effectiveness

The reasons for study exclusion are provided in brackets.

Albertsson-Wikland K, Alm F, Aronsson S, Gustafsson J, Hagenas L, Hager A, *et al.* Effect of growth hormone (GH) during puberty in GH-deficient children: preliminary results from an ongoing randomised trial with different dose regimens. *Acta Paediatr* 1999;**88**:80–4.
[No untreated group.]

Bertrand AM, Chaussain JL, Job B, Mariani R, Ponte C, Rappaport R, *et al.* Three years of GH treatment in Turner's syndrome: complex effect of GH dosage on growth parameters. *Clin Endocrinol* 1996;**44**:665–71.
[No untreated group.]

Blethen SL, Baptista J, Kuntze J, Foley T, LaFranchi S, Johanson A. Adult height in growth hormone (GH)-deficient children treated with biosynthetic GH. The Genentech Growth Study Group. *J Clin Endocrinol Metab* 1997;**82**:418–20.
[No untreated group, $n < 300$.]

Cacciari E, Cicognani A, Pirazzoli P, Zucchini S, Salardi S, Balsamo A, *et al.* Final height of patients treated for isolated GH deficiency: examination of 83 patients. *Eur J Endocrinol* 1997;**137**:53–60.
[Untreated group did not have condition of interest.]

Cassorla F, Mericq V, Eggers M, Avila A, Garcia C, Fuentes A, *et al.* Effects of luteinizing hormone-releasing hormone analog-induced pubertal delay in growth hormone (GH)-deficient children treated with GH: preliminary results. *J Clin Endocrinol Metab* 1997;**82**:3989–92.
[No untreated group.]

Chen RG, Shen YN, Yei J, Wang CF, Xie DH, Wang XH, *et al.* A comparative study of growth hormone (GH) and GH-releasing hormone(1-29)-NH2 for stimulation of growth in children with GH deficiency. *Acta Paediatr Suppl* 1993;**388**:32–5.
[No untreated group.]

Chernausek SD, Attie KM, Cara JF, Rosenfeld RG, Frane J. Growth hormone therapy of Turner syndrome: the impact of age of oestrogen replacement on final height. Genentech, Inc., Collaborative Study Group. *J Clin Endocrinol Metab* 2000;**85**:2439–45.
[No untreated group.]

de Muinck Keizer-Schrama S, Rikken B, Hokken KA, Wit JM, Drop S. Comparative effect of two doses of growth hormone for growth hormone deficiency. *Arch Dis Child* 2000;**71**:12–18.
[No untreated group.]

de Muinck Keizer-Schrama SMPF, Sas TCJ. Growth hormone treatment regimens in girls with Turner syndrome. Dutch Advisory Group on Growth Hormone. *Acta Paediatr Suppl* 1999;**88**(Suppl 433):126–9.
[No untreated group.]

de Muinck Keizer-Schrama S, Van den Broeck J, Sas T, Hokken KA. Final height of growth hormone-treated GH-deficient children and girls with Turner's syndrome: the Dutch experience. The Dutch Advisory Group on Growth Hormone. *Horm Res* 1999;**51**(Suppl 3):127–31.
[GHD: no untreated group, $n < 300$; TS: no untreated group.]

De Schepper J, Craen M, Massa G, Heinrichs C, Maes M, Du CM, *et al.* Growth hormone therapy in Turner's syndrome: one versus two daily injections. *J Clin Endocrinol Metab* 1994;**79**:489–94.
[No untreated group.]

The Genentech Collaborative Study Group. Response to growth hormone in children with idiopathic short stature. *Acta Paediatr Scand Suppl* 1990;**366**:24–6.
[Results reported in another included study.[38]]

Guest G, Berard E, Crosnier H, Chevallier T, Rappaport R, Broyer M. Effects of growth hormone in short children after renal transplantation. *Pediatr Nephrol* 1998;**12**:437–46.
[Subset of patients from another included study.[31]]

Haeusler G, Frisch H, Schmitt K, Blumel P, Plochl E, Zachmann M, *et al.* Treatment of patients with Ullrich–Turner syndrome with conventional doses of growth hormone and the combination with testosterone or oxandrolone: effect on growth, IGF-I and IGFBP-3 concentrations. *Eur J Pediatr* 1995;**154**:437–44.
[No untreated group.]

Hokken-Koelega ACS, Stijnen T, De Jong MCJW, Donckerwolcke RA, de Muinck Keizer-Schrama SMPF, Blum WF, *et al.* Double-blind trial comparing the effects of two doses of growth hormone in prepubertal patients with chronic renal insufficiency. *J Clin Endocrinol Metab* 1994;**79**:1185–90.
[No untreated group.]

Hokken-Koelega AC, Stijnen T, de Ridder MA, de Muinck Keizer-Schrama SM, Wolff ED, De Jong MC, *et al.* Growth hormone treatment in growth-retarded adolescents after renal transplant. *Lancet* 1994; **343**:1313–17.
[No untreated group.]

Hopwood NJ, Hintz RL, Gertner JM, Attie KM, Johanson AJ, Baptista J, *et al.* Growth response of children with non-growth-hormone deficiency and marked short stature during three years of growth hormone therapy. *J Pediatr* 1993;**123**:215–22.
[Results reported in another included study.[38]]

Ito RK, Vig KW, Garn SM, Hopwood NJ, Loos PJ, Spalding PM, *et al.* The influence of growth hormone (rhGH) therapy on tooth formation in idiopathic short statured children. *Am J Orthod Dentofacial Orthop* 1993;**103**:358–64.
[Growth not primary outcome.]

Job JC, Landier F. Three-year results of treatment with growth hormone, alone or associated with oxandrolone, in girls with Turner syndrome. *Horm Res* 1991;**35**:229–33.
[No untreated group.]

Job JC, Toublanc JE, Landier F. Growth of short normal children in puberty treated for 3 years with growth hormone alone or in association with gonadotropin-releasing-hormone agonist. *Horm Res* 1994;**41**:177–84.
[No untreated group.]

Johnston DI, Betts P, Dunger D, Barnes N, Swift PGF, Buckler JMH, *et al.* A multi-centre trial of recombinant growth hormone and low dose oestrogen in Turner syndrome: near final height analysis. *Arch Dis Child* 2001;**84**:76–81.
[No untreated group.]

Kawaguchi H, Ito K. rhGH use in children with CRI and undergoing dialysis post-transplant in Japan: a multi-centre study. MultiCenter Study Group Japan. *Br J Clin Pract Suppl* 1996;**85**:26–31.
[No untreated group.]

Lindgren AC, Ritzen EM. Five years of growth hormone treatment in children with Prader–Willi syndrome. Swedish National Growth Hormone Advisory Group. *Acta Paediat Suppl* 1999;**88**:109–11.
[No untreated group at final height and incomplete final height data.]

Loche S, Pintor C, Cambiaso P, Lampis A, Carta D, Corda R, *et al.* The effect of short-term growth hormone or low-dose oxandrolone treatment in boys with constitutional growth delay. *J Endocrinol Invest* 1991;**14**:747–50.
[No untreated group.]

MacGillivray MH, Baptista J, Johanson A. Outcome of a four-year randomized study of daily versus three times weekly somatropin treatment in prepubertal naive growth hormone-deficient children. Genentech Study Group. *J Clin Endocrinol Metab* 1996;**81**:1806–9.
[No untreated group.]

Massa G, Otten BJ, de Muinck Keizer-Schrama SM, Delemarre-van de Waal HA, Jansen M, Vulsma T, *et al.* Treatment with two growth hormone regimens in girls with Turner syndrome: final height results. Dutch Growth Hormone Working Group. *Horm Res* 1995;**43**:144–6.
[No untreated group.]

Maxwell H, Rees L. Randomised controlled trial of recombinant human growth hormone in prepubertal and pubertal renal transplant recipients. *Arch Dis Child* 1998;**79**:481–7.
[Subset of patients from another included study.[31]]

Mericq MV, Eggers M, Avila A, Cutler GB Jr, Cassorla F. Near final height in pubertal growth hormone (GH)-deficient patients treated with GH alone or in combination with luteinizing hormone-releasing hormone analog: results of a prospective, randomized trial. *J Clin Endocrinol Metab* 2000;**85**:569–73.
[No untreated group.]

Neyzi O, Yordam N, Ocal G, Bundak R, Darendeliler F, Acikgoz E, *et al.* Growth response to growth hormone-releasing hormone(1-29)-NH2 compared with growth hormone. *Acta Paediatr Suppl* 1993;**388**:16–21.
[No untreated group.]

Nilsson KO, Albertsson-Wikland K, Alm J, Aronson S, Gustafsson J, Hagenas L, *et al.* Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. *J Clin Endocrinol Metab* 1996;**81**:635–40.
[No untreated group.]

Phillip M, Hershkovitz E, Belotserkovsky O, Leiberman E, Limoni Y, Zadik Z. Once versus twice daily injections of growth hormone in children with idiopathic short stature. *Acta Paediatr* 1998;**87**:518–20.
[No untreated group.]

Rekers-Mombarg LTM, Massa GG, Wit JM, Matranga AMC, Buckler JMH, Butenandt O, *et al.* Growth hormone therapy with three dosage regimens in children with idiopathic short stature. *J Pediatr* 1998;**132**:455–60.
[No untreated group.]

Rongen-Westerlaken C, Vanes A, Wit JM, Otten BJ, de Muinck Keizer-Schrama SMPF, Drayer NM, *et al.* Growth hormone therapy in Turners syndrome – impact of injection frequency and initial bone-age. *Am J Dis Child* 1992;**146**:817–20.
[No untreated group.]

Rosenfeld RG. Growth hormone therapy in Turner's syndrome: an update on final height. Genentech National Cooperative Study Group. *Acta Paediatr Suppl* 1992;**383**:3–6.
[No untreated group at final height.]

Rosenfeld RG, Attie KM, Frane J, Brasel JA, Burstein S, Cara JF, *et al.* Growth hormone of Turner's syndrome: beneficial effect on adult height. *J Pediatr* 1998;**132**:319–24.
[No untreated group at final height.]

Rosenfeld RG, Frane J, Attie KM, Brasel JA, Burstein S, Cara JF, *et al.* Six-year results of a randomized, prospective trial of human growth hormone and oxandrolone in Turner syndrome. *J Pediatr* 1992;**121**:49–55.
[No untreated group after 12–24 months.]

Saenger P, Baptista J. Effects of high dose rhGH therapy in adolescent children with GH deficiency: a randomized, multicenter study. *Horm Res (Basel)* 1998;**50**:10.
[No untreated group.]

Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, Jansen M, Otten BJ, Hoorweg-Nijman JJ, *et al.* Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: results of a randomized dose–response trial. *J Clin Endocrinol Metab* 1999;**84**:4607–12.
[No untreated group.]

Sas TC, de Muinck Keizer-Schrama SM, Stijnen T, van Teunenbroek A, Hokken-Koelega AC, Waelkens JJ, *et al.* Final height in girls with Turner's syndrome treated with once or twice daily growth hormone injections. Dutch Advisory Group on Growth Hormone. *Arch Dis Child* 1999;**80**:36–41.
[No untreated group.]

Sas TCJ, Gerver WJM, de Bruin R, Stijnen T, de Muinck Keizer-Schrama SMPF, Cole TJ, *et al.* Body proportions during long-term growth hormone treatment in girls with Turner syndrome participating in a randomized dose–response trial. *J Clin Endocrinol Metab* 1999;**84**:4622–8.
[No untreated group.]

Stahnke N, Stubbe P, Keller E, Amendt P, Bramswig J, Butenandt O, *et al.* Recombinant human growth hormone and oxandrolone in treatment of short stature in girls with Turner syndrome. *Horm Res* 1992;**37**:37–46.
[No untreated group.]

Stanhope R, Uruena M, Hindmarsh P, Leiper AD, Brook CG. Management of growth hormone deficiency through puberty. *Acta Paediatr Scand Suppl* 1991;**372**:47–52.
[No untreated group.]

Thompson RG, Conforti P, Holcombe J. Biosynthetic human growth hormone: current status and future questions. *J Endocrinol Invest* 1989;**12**:35–9.
[No untreated group.]

Vanderschueren LM, Massa G, Maes M, Craen M, Van Vliet G, Heinrichs C, *et al.* Growth-promoting effect of growth hormone and low dose ethinyl estradiol in girls with Turner's syndrome. *J Clin Endocrinol Metab* 1990;**70**:122–6.
[No untreated group.]

Van Teunenbroek A, de Muinck Keizer-Schrama SMPF, Stijnen T, Jansen M, Otten BJ, Delemarre-van de Waal HA, *et al.* Yearly stepwise increments of the growth hormone dose results in a better growth response after four years in girls with Turner syndrome. *J Clin Endocrinol Metab* 1996;**81**:4013–21.
[No untreated group.]

Van Teunenbroek A, de Muinck Keizer-Schrama S, Stijnen T, Waelkens J, Wit JM, Vulsma T, *et al.* Growth response and levels of growth factors after two years growth hormone treatment are similar for a once and twice daily injection regimen in girls with Turner syndrome. Dutch Working Group on Growth Hormone. *Clin Endocrinol (Oxf)* 1997;**46**:451–9.
[No untreated group.]

Wit JM, Boersma B, de Muinck Keizer-Schrama SM, Nienhuis HE, Oostdijk W, Otten BJ, *et al.* Long-term results of growth hormone therapy in children with short stature, subnormal growth rate and normal growth hormone response to secretagogues. Dutch Growth Hormone Working Group. *Clin Endocrinol (Oxf)* 1995;**42**:365–72.
[Non-randomised controls.]

Wit JM, Kamp GA, Rikken B. Spontaneous growth and response to growth hormone treatment in children with growth hormone deficiency and idiopathic short stature. *Pediatr Res* 1996;**39**:295–302.
[Non-systematic review.]

Economics literature review

None of these references provided data that could be used in a cost–utility analysis.

Boulton TJC, Dunn SM, Quigley CA, Taylor JJ, Thompson L. Perception of self and short stature: effects of two years of growth hormone treatment. *Acta Paediatr Scand Suppl* 1991;**377**:20–7.

Busschbach JJ, Rikken B, Grobbee DE, De Charro FT, Wit JM. Quality of life in short adults. *Horm Res* 1998;**49**:32–8.

Downie AB, Mulligan J, McCaughey ES, Stratford RJ, Betts PR, Voss LD. Psychological response to growth hormone treatment in short normal children. *Arch Dis Child* 1996;**75**:32–5.

Downie AB, Mulligan J, Stratford RJ, Betts PR, Voss LD. Are short normal children at a disadvantage? The Wessex Growth Study. *BMJ* 1997;**314**:97–100.

Lagrou K, Xhrouet HD, Heinrichs C, Craen M, Chanoine JP, Malvaux P, *et al.* Age-related perception of stature, acceptance of therapy, and psychosocial functioning in human growth hormone-treated girls with Turner's syndrome. *J Clin Endocrinol Metab* 1998;**83**:1494–501.

Leiberman E, Pilpel D, Carel CA, Levi E, Zadik Z. Coping and satisfaction with growth hormone treatment among short-stature children. *Horm Res* 1993;**40**:128–35.

Okada Y. The quality of life of Turner women in comparison with grown-up GH-deficient women. *Endocr J* 1994;**41**:345–54.

Pilpel D, Leiberman E, Zadik Z, Carel CA. Effect of growth hormone treatment on quality of life of short-stature children. *Horm Res* 1995;**44**:1–5.

Postlethwaite RJ, Eminson DM, Reynolds JM, Wood AJ, Hollis S. Growth in renal failure: a longitudinal study of emotional and behavioural changes during trials of growth hormone treatment. *Arch Dis Child* 1998;**78**:222–9.

Rekers-Mombarg LT, Busschbach JJ, Massa GG, Dicke J, Wit JM. Quality of life of young adults with idiopathic short stature: effect of growth hormone treatment. Dutch Growth Hormone Working Group. *Acta Paediatr* 1998;**87**:865–70.

Rikken B, van Busschbach J, le Cessie S, Manten W, Spermon T, Grobbee R, *et al.* Impaired social status of growth hormone deficient adults as compared to controls with short or normal stature. *Clin Endocrinol* 1995;**43**:205–11.

Sandberg DE, Brook AE, Campos SP. Short stature: a psychosocial burden requiring growth hormone therapy? *Pediatrics* 1994;**94**:832–40.

Singh J, Cuttler L, Shin M, Silvers JB, Neuhauser D. Medical decision-making and the patient: understanding preference patterns for growth hormone therapy using conjoint analysis. *Med Care* 1998;**36**:AS31–45.

Takano K, Tanaka T, Saito T. Psychosocial adjustment in a large cohort of adults with growth hormone deficiency treated with growth hormone in childhood: summary of a questionnaire survey. Committee for the Study Group of Adult GH Deficiency. *Acta Paediatr Suppl* 1994;**399**:16–19.

Teeling-Smith G, West R. Economic evaluation of growth hormone therapy. *OHE Briefing* 1991; No. 28.

Zimet GD, Cutler M, Litvene M, Dahms W, Owens R, Cuttler L. Psychological adjustment of children evaluated for short stature: a preliminary report. *J Dev Behav Pediatr* 1995;**16**:264–70.

Zimet GD, Owens R, Dahms W, Cutler M, Litvene M, Cuttler L. Psychosocial outcome of children evaluated for short stature. *Arch Pediatr Adolesc Med* 1997;**151**:1017–23.

Appendix 7

Outcome measures

Primary outcomes used in assessment of effectiveness

The primary outcome measures used in the assessment of effectiveness include:

- **height**: standing height measure (cm) at a given point in time (e.g. after some period of treatment)
- **height standard deviation score (HtSDS)**: height relative to norms for children of the same age
- **final height (cm or SDS)**: height at completion of growth expressed in cm or relative to adult norms
- **growth velocity (GV)**: change in height over a given time period (e.g. cm/year)
- **GVSDS**: GV relative to norms for children of the same age
- **bone age**: a measure of skeletal maturity
- **body composition**: a group of measures that assess obesity and amount of fat relative to other body tissues
- **psychological**: measures that indicate whether treatment affects psychological factors.

Height measurement

Height (and GV; see below) may be expressed in length units (e.g. cm) or in SDS. SDS using controlled data collected from an appropriate population base allows comparison of measures independent of age or sex. In this system, the normal population mean is zero, and a normal SDS will lie between –2 and +2 SD (see *Figure 1* in chapter 1). A healthy individual's SDS will not change during the growth years. Increased SDS implies catch-up growth, and a decrease implies growth failure.

Height, growth and virtually any other measure can be considered either in terms of absolute values (e.g. final height = 160 cm) or in terms of change from a baseline value (e.g. ΔHtSDS = 1.2). Either can be valid measures in the context of a study comparing scores between treated and untreated groups. However, sometimes changes are analysed as before and after measures within groups. Within-group before and after comparisons should be treated with caution because many factors can be confounded with the treatment effect, including changes due to maturation (e.g. the onset of puberty), changes due to history and other effects such as seasonal variation in growth in short-term studies. When change scores have been assessed within groups rather than between groups, this has been noted in the text.

When height is considered relative to population norms, appropriate norms should be used. New charts compiled from measurements of 300,000 children are now considered representative of UK children today and should be used in preference to Tanner–Whitehouse charts compiled in the 1960s. The new charts show that children are taller by a full percentile over measures from 30 years ago.[94]

This issue is relevant to considering final height results from studies that compare results with historical controls (who may all have been shorter than a contemporary cohort). It is also relevant to considering final height results from studies that compare final height with height predictions based on models that used older normative height data.

Final height

The best measure of how GH affects growth is to measure final adult height (in cm or SD). In the best designs, final height in a group treated with GH would be compared with final height in children randomised to receive a placebo treatment or no treatment (an RCT).

Rather than randomising children into treatment and control groups, some studies compare the final height in a single group of GH-treated children with children who were untreated in the past (historical controls). Ideally, this group should be as similar as possible to the treated group, including being evaluated as recently as possible and being drawn from the same country of origin (because there are geographical variations in height). However, because height has been steadily increasing in the general population over time, the use of historical controls can substantially overestimate the effects of GH treatment. In addition, the use of databases of children treated with GH has been criticised because it ignores the fact that RCTs generally find lower estimates of treatment effects across areas of medicine than do observational studies, use of historical controls or non-randomised

contemporary controls.[95] Finally, the databases may not include all the relevant parameters for all patients, and therefore particular comparisons may be based on small samples despite coming from large databases.

Obviously, measuring final height requires that the child has finished growing. The most reliable measures of final height use multiple criteria to determine that growth is complete or nearly complete. Generally, it is considered that children have completed or nearly completed their growth when their growth rate within a year has slowed to less than some specified amount (e.g. 1–2 cm) and skeletal maturity assessed by radiographs of the wrist and hand indicate that the epiphyses have closed (often expressed as BA more than a certain value, e.g. 14–15 years). Trials that use a poor definition for final height may give unreliable estimates of the effects of GH by measuring participants before their growth is complete. Sometimes studies report 'near final height' (NFH). Generally, NFH is a measure of height when it is presumed that growth is complete as discussed above, but acknowledges that growth may not be complete. Although comparisons of NFH between treated and untreated children would be valid (assuming a good trial design), comparisons between treated children and historical controls or height norms may not provide a good estimate of treatment effects.

Predicting height

Measuring final height generally requires that trials continue for several years and ideally include an untreated group. Because of both these constraints, some studies have used methods of calculating what a child's height might have been if they were untreated. These methods allow children to serve in some sense as their own controls, with outcomes consisting of changes from predicted heights. In addition, studies can be reported more quickly and do not need to include an untreated group. The current report summarises predicted height outcomes when they are reported in the included trials (see appendices 11–20). However, the evaluations in the main text are not based on these predictions, and therefore these outcomes will not be considered in detail here.

There have been serious criticisms of outcome measures that are intended to be surrogates for final height. Height prediction models have not been validated in many of the specific conditions being treated.[95] Prediction models should be specific by condition or validated within conditions.

Predicted adult height (PAH) is a measure that is commonly used. This method estimates adult height by extrapolating from childhood measurements either using a regression equation or assuming that untreated children will maintain the same height percentile into adulthood.[61] Height gain is expressed as final height minus PAH. One height prediction model often used in studies of TS was developed by Lyon and co-workers.[7] The generalisability of this model has been questioned because it was based on a small sample that included only one patient who was taller than the 75th percentile on the TS-specific growth chart. The model was not found to be as accurate when applied to other case series.[49]

There are also models that predict final height from BA calculations. These models are based on the growth of normal children, and strictly speaking they were not designed to be applied to children with the conditions being considered. They may not even be valid for children with severe short stature of undefined aetiology[75] because they have been found to overestimate height in boys with ISS[6,92] and to underestimate height in some girls with ISS.[92] Their use has been criticised in conditions such as TS in which there is a degree of skeletal dysplasia.[61]

It has been suggested that treatment effects that are based on predicted heights can give different results based upon the particular reference data used for the prediction.[96] For this reason, it has been suggested that final heights at the end of therapy be used to assess treatment effects.[96]

Sometimes height is compared with that of the midpoint of parents' heights ('target height'). There is a 95% probability that the final height of a normal child will be within ± 8.5 cm of the height predicted from parental measurements.[97] Comparison of predicted height with target height can be used to assess whether a child is experiencing growth failure. Children with growth failure, such as untreated girls with TS, generally do not achieve a final height within the mid-parental target range. Final heights that are in the target range are taken to be suggestive of an enhancing effect of treatment. However, this is a very crude measure.

Growth velocity

Although the overall effectiveness of GH in treating short stature is to be found in measures of final height, it has been argued that short-term measures of growth are also of importance. Children and parents may be concerned with

whether growth within a certain time frame is comparable to that of a child's peers. Velocity may also be a better interim growth measure than height attained at a particular age because it is independent of growth in previous years. GV is also used to assess the response of children to treatment.

GV is a measure of the height gained (cm) within a specified time period (usually a year). This outcome is also often referred to as 'height velocity'. GV can also be considered in relation to a child's age by considering GV relative to the distribution of GVs for children of a particular age (GVSDS). As with height, GVSDS measures are dependent upon the reference data used.[96]

BA

BA is a measure of skeletal maturity. It is customarily determined by examining the relative positions of the bones in the left hand and wrist in a radiograph. The measurement of BA relative to chronological age is important in height prediction models. In addition, BA assessments are used to evaluate when the epiphyses have closed and growth is complete. The interim assessment of BA is important in determining whether treatment is advancing bone maturity such that short-term GV might come at the expense of early closure of the epiphyses.

Body composition

In some conditions (e.g. GHD and PWS), the potential effects of GH on body composition may be as salient to children and parents as effects on growth. In trials that measured body composition in ways that would be salient to participants, those effects are summarised in data extraction tables (see appendix 17). These measures include BMI, lean body mass and per cent body fat. Although these measures have been included in data extractions, the primary emphasis in the current report is on growth measures, and therefore these measures will not be discussed in detail.

BMI (kg/m^2) is widely used as a measure of obesity. Lean body mass (fat-free mass) and percent body fat are measures of how much of body weight is in fat versus other tissues.

Psychological measures

It is of considerable interest to determine whether treatment with GH affects children's sense of well-being or quality of life. A number of measures have been designed to assess quality of life in ways that can be used in economic assessment. In addition, there are many measures of self-concept, psychosocial functioning and so on that might be affected by GH treatment.

Some of the conditions being considered include psychological or cognitive characteristics. It is of interest to determine whether GH treatment might affect cognitive functioning. This might be particularly relevant in TS, for instance, in which visuospatial performance is sometimes affected. Likewise, PWS generally involves psychological symptoms such as obsession or depression as well as behavioural problems. It would therefore be of interest to determine whether treatment would affect these psychological and behavioural symptoms.

Other physiological measures

Many studies included measures of various hormones, glucose, cholesterol and so on. Such measures are important for assessing the biochemical and metabolic effects of GH, and might be of great long-term importance to health. However, they are generally not outcomes that would be salient in the short term to the patients themselves. Therefore, these measures have not been included in the assessments of clinical effectiveness. Some of these measures are relevant for assessing adverse effects such as diabetes mellitus. Chapter 9 is devoted to a discussion of adverse effects.

Appendix 8

Feasibility of obtaining QALY weights among members of the Turner Syndrome Support Society, UK

This appendix provides a synopsis of some feasibility work undertaken to consider whether a close approximation for valuing the gains in quality of life (QoL) achieved by GH treatment could be made within the constraints available. The thinking behind this was that cost–utility analysis is probably a more appropriate framework for evaluating GH treatment in children suffering from the conditions of interest, but no existing data were available to inform a cost–utility approach.

Although there was inconclusive evidence from the literature review that QoL with GH treatment improved, there is clear evidence that treatment can have potentially significant effects for individual patients. In addition, parents and children value quite highly the availability of the treatment.[14,15] An alternative way to obtain utility weights to inform a cost–utility analysis would be to ask patients to describe health-related QoL associated with and without treatment by using a standardised instrument that converts to utility weights using a social tariff.

An adviser for the TSSS, UK, approached the research team to ask us to explore the possibility of conducting a one-off survey of QoL among the members of the society to inform the utility of GH treatment in children or at least in children with TS. Two key preliminary factors were explored to assess the feasibility of conducting such a survey: (1) whether a suitable 'off-the-shelf' QoL instrument existed that was validated for use as a self-administered questionnaire among children or their parents/guardians, and (2) whether the number and diagnostic/treatment mix of members of TSSS would provide sufficient power to show valid results.

QoL instruments

Suitable QoL instruments would need to be validated for use with children/parents, be self-administered, provide a single utility value and be sensitive enough to pick the main QoL effects of interest. The instruments investigated were the EuroQoL-5 dimensions (EQ-5D),[98,99] Health Utility Index (HUI)-Mark 2/HUI-Mark 3,[98,100,101] 15-, 16- and 17-dimensional health-related measures (15D/16D/17D),[98,102,103] and Quality of Well-being (QWB) Scale.[104] Unfortunately, not one of them met the full set of criteria. The main objections for application of these instruments for the purposes of this review are presented in *Table 45*.

TSSS members: study sample

It was necessary to assess some background details about the potential of TSSS members to serve as a sampling frame. Closer inspection revealed a broad mix of characteristics among the 350 members of TSSS. The membership comprised both parents and children of various age groups, and the children had a wide range of experiences regarding treatment (both with GH and other treatments). Although background factors could be controlled for, it would have required a larger sampling frame to show smaller but important QoL differences, and this was not viable within the constraints of the review.

Other issues considered were that QoL valuation for GH-treated and non-treated patients would be obtained with questionable comparability, no data were available to investigate how representative TSSS members are of society, and the potential generalisability of results to other patient populations would be unknown.

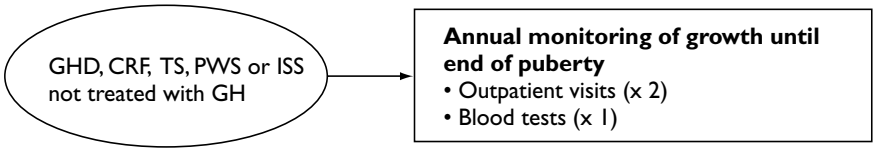
TABLE 45 *QoL instruments investigated: strengths and weaknesses*

QoL instrument	Strengths	Weaknesses
EQ-5D	• UK valuation exists • Available free of charge for public sector application	• Non-validated for use in children • Non-validated for use with parents/ guardians as proxies • Potentially not sensitive enough to pick up important psychosocial QoL aspects
HUI-Mark 2/ HUI-Mark 3	• Battery of instruments for different age groups • Valued by Canadian population	• HUI-Mark 3 administered by phone only • Not valued in UK • Not available free of charge for public sector application
15D/16D/17D	• Potentially sensitive battery of instruments • Valued by Finnish population	• English language versions of 16D/17D under validation • Not valued in UK • 17D questionnaire is interviewer administered
QWB	• US valuation	• Not valued in UK • Self-administered questionnaire is not validated • Scale is not modified for children • Potentially not sensitive enough to pick up important psychosocial QoL aspects

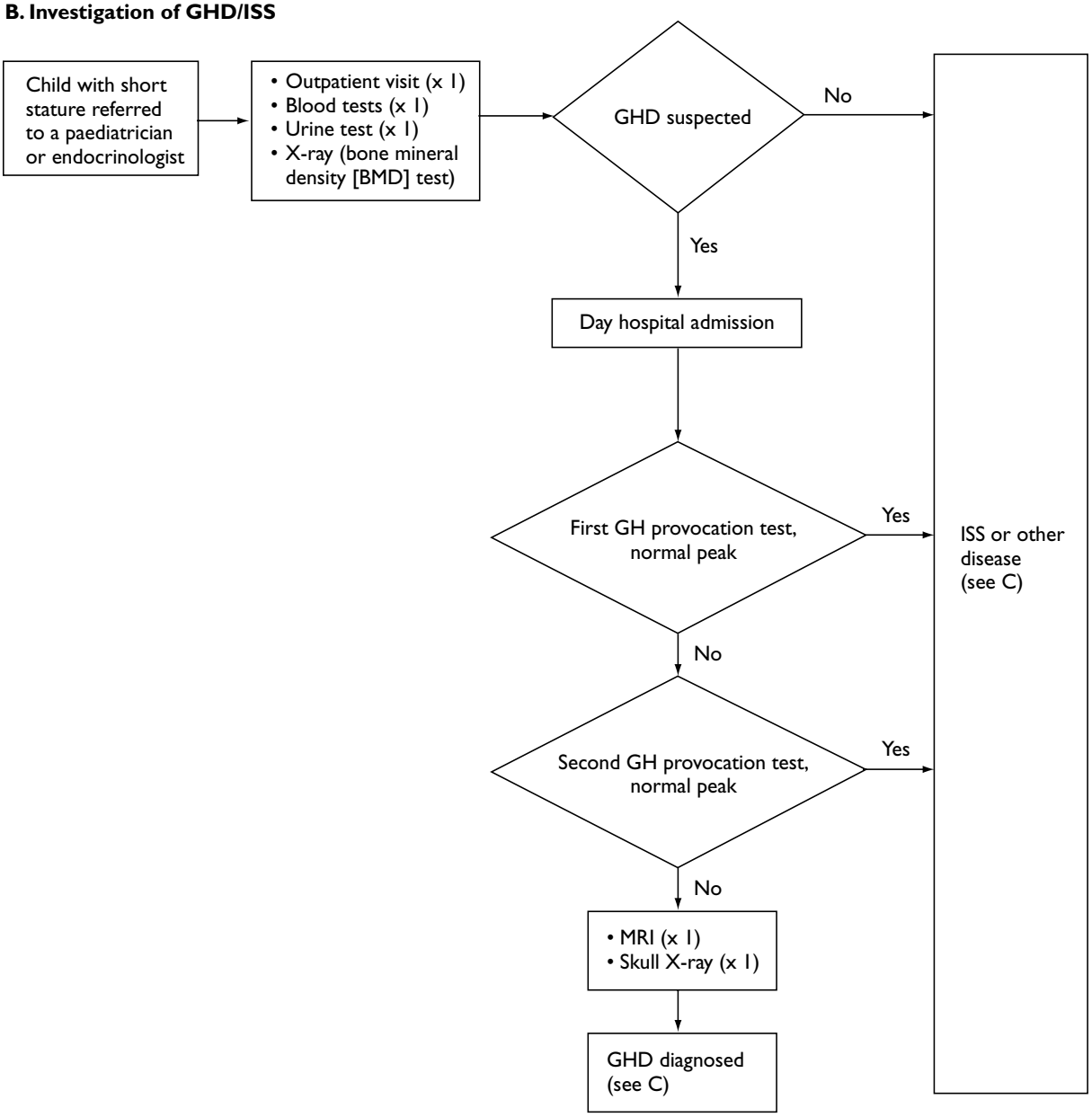
Appendix 9

Event pathways for children with GHD, CRF, TS, PWS or ISS

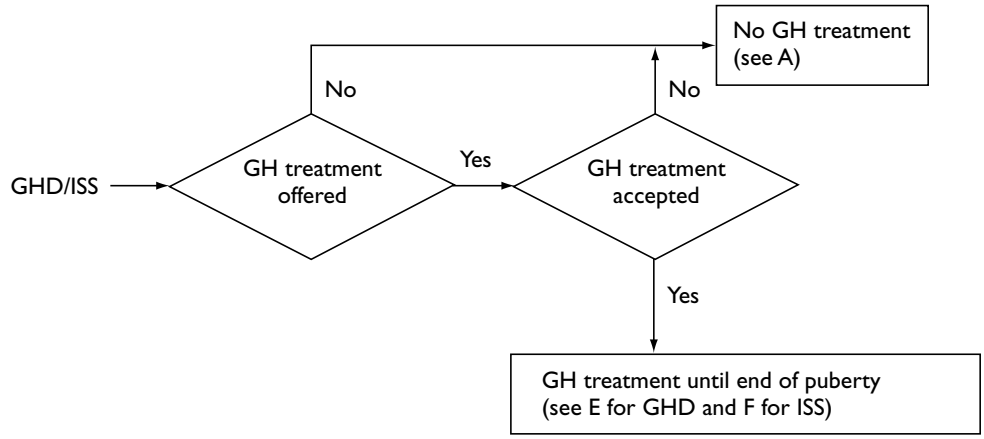
A. No GH treatment



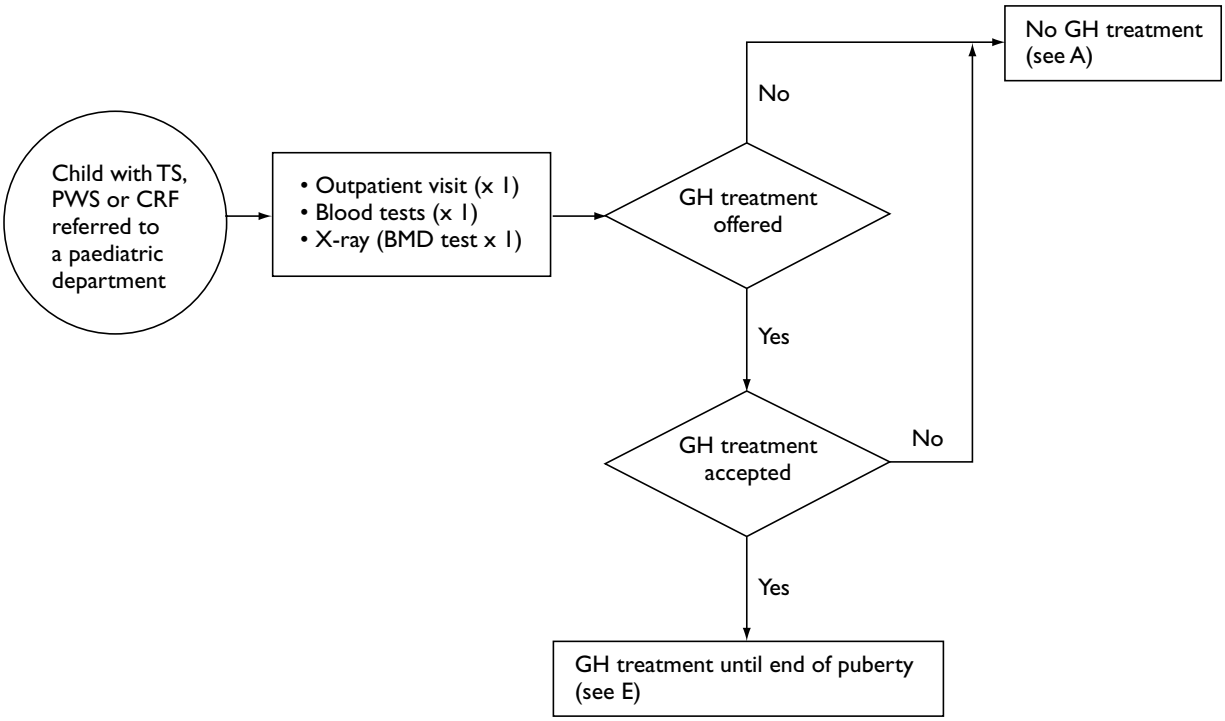
B. Investigation of GHD/ISS



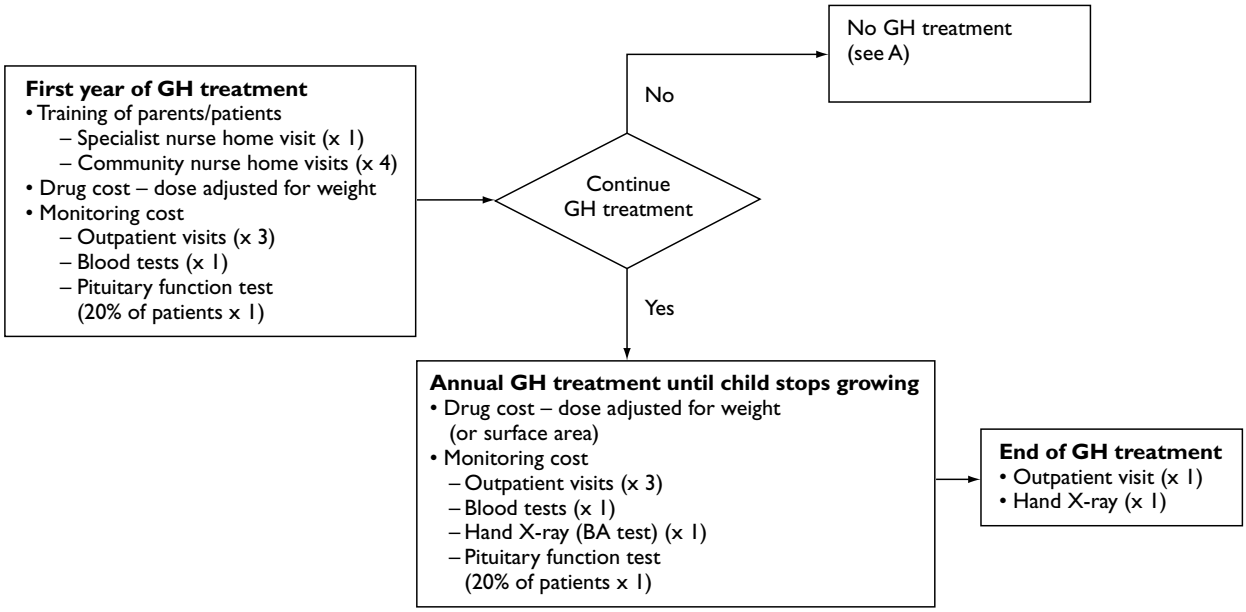
C. GH treatment decision for children with GHD or ISS



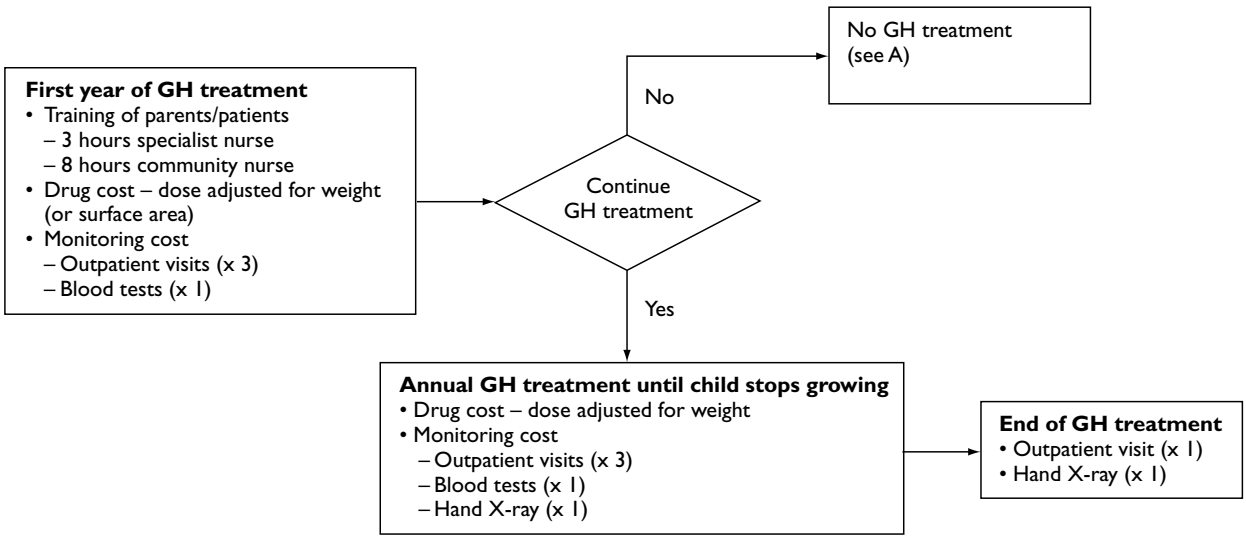
D. GH treatment decision for children with TS, PWS or CRF



E. GH treatment for children with GHD (administered until end of puberty)



F. GH treatment for children with ISS, TS, CRF or PSW (administered until end of puberty)



Appendix 10

Sensitivity analyses

A range of sensitivity analyses were performed in order to assess the impact of uncertainty on the model. These included one-way sensitivity analysis on seven critical model parameters (length of treatment, continuation with treatment, FH effect, GH dose, GH cost, and discount rates for benefits and costs) and two-way sensitivity analysis on two potentially important sets of interactions (drug dose and effectiveness, and length of treatment and effectiveness). The parameters selected were based on anticipating which ones could expect to have the largest possible impact on the model. The range of uncertainty tested used the most reliable source of information available.

GHD

Base case 1

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	8 years	1–13 years	£1,385	£6,745
Continuance of treatment	71%	30–100%	£5,952	£6,032
Incremental FH effect (change compared with base value)	100%	70–300%	£2,010	£8,613
GH dose	0.175 mg/kg/week	0.14–0.35 mg/kg/week	£4,864	£11,853
GH cost	£20.82	£15–25	£4,401	£7,198
Annual rate of discounting for benefits	1.5%	0–6%	£5,722	£7,034
Annual rate of discounting for costs	6%	0–12%	£4,795	£7,632
ICER	£6,029		£1,385	£11,853
Two-way sensitivity analysis				
GH dose	0.175 mg/kg/week	0.14–0.35 mg/kg/week		
FH effect	100%	70–300%	£1,621	£16,933
Length of treatment	8 years	1–13 years		
FH effect	100%	70–300%	£462	£9,636

Base case 2

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	5 years	1–13 years	£1,660	£8,090
Continuance of treatment	71%	30–100%	£5,781	£5,705
Incremental FH effect (change compared with base value)	100%	70–300%	£1,903	£8,155
GH dose	0.175 mg/kg/week	0.14–0.35 mg/kg/week	£4,608	£11,209
GH cost	£20.82	£15–25	£4,171	£6,813
Annual rate of discounting for benefits	1.5%	0–6%	£5,540	£6,245
Annual rate of discounting for costs	6%	0–12%	£5,020	£6,491
ICER	£5,708		£1,660	£11,209
Two-way sensitivity analysis				
Drug dose	0.175 mg/kg/week	0.14–0.35 mg/kg/week		
FH effect	100%	70–300%	£1,536	£16,013
Length of treatment	5 years	1–13 years		
FH effect	100%	70–300%	£553	£11,557

TS

Base case 1

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	5 years	1–13 years	£4,690	£22,339
Continuance of treatment	87%	30–100%	£16,914	£15,886
Incremental FH effect (change compared with base value)	100%	70–300%	£5,326	£22,824
GH dose	0.30 mg/kg/week	0.175–0.7 mg/kg/week	£9,432	£36,855
GH cost	£20.82	£15.25–25	£11,592	£19,126
Annual rate of discounting for benefits	1.5%	0–6%	£15,504	£17,480
Annual rate of discounting for costs	6%	0–12%	£14,109	£18,099
ICER	£15,977		£4,690	£36,855
Two-way sensitivity analysis				
GH dose	0.30 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	70–300%	£3,144	£52,649
Length of treatment	1–13 years	1–13 years		
FH effect	100%	70–300%	£1,563	£31,801

Base case 2

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	5 years	1–13 years	£5,116	£24,369
Continuance of treatment	87%	30–100%	£18,451	£17,331
Incremental FH effect (change compared with base value)	100%	70–300%	£5,810	£24,899
GH dose	0.30 mg/kg/week	0.175–0.7 mg/kg/week	£10,289	£40,205
GH cost	£20.82	£15.25–25	£12,646	£20,864
Annual rate of discounting for benefits	1.5%	0–6%	£16,914	£19,069
Annual rate of discounting for costs	6%	0–12%	£15,391	£19,744
ICER	£17,429		£5,116	£40,205
Two-way sensitivity analysis				
GH dose	0.30 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	70–300%	£3,430	£57,436
Length of treatment	5 years	1–13 years		
FH effect	0.30 mg/kg/week	70–300%	£1,705	£34,692

CRF

Base case 1

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	3 years	1–13 years	£3,095	£14,665
Continuance of treatment	84%	30–100%	£8,172	£7,335
Incremental FH effect (change compared with base value)	100%	70–300%	£2,468	£10,576
GH dose	0.33 mg/kg/week	0.175–0.7 mg/kg/week	£3,965	£15,530
GH cost	£20.82	£15.25–25	£5,364	£8,868
Annual rate of discounting for benefits	1.5%	0–6%	£7,293	£7,748
Annual rate of discounting for costs	6%	0–12%	£6,970	£7,856
ICER	£7,403		£2,468	£15,530
Two-way sensitivity analysis				
GH dose	0.33 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	70–300%	£1,322	£22,185
Length of treatment	3 years	1–13 years		
FH effect	100%	70–300%	£1,032	£20,858

Base case 2

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	5 years	1–13 years	£7,455	£33,619
Continuance of treatment	84%	30–100%	£25,304	£23,985
Incremental FH effect (change compared with base value)	100%	70–300%	£8,031	£34,418
GH dose	0.33 mg/kg/week	0.175–0.7 mg/kg/week	£12,902	£50,538
GH cost	£20.82	£15.25–25	£17,458	£28,858
Annual rate of discounting for benefits	1.5%	0–6%	£23,381	£26,360
Annual rate of discounting for costs	6%	0–12%	£21,194	£27,393
ICER	£24,093		£7,455	£50,538
Two-way sensitivity analysis				
GH dose	0.33 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	70–300%	£4,301	£72,197
Length of treatment	5 years	1–13 years		
FH effect	100%	70–300%	£2,485	£47,845

PWS

Base case 1

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	5 years	1–13 years	£10,873	£58,266
Continuance of treatment	100%	30–100%	£40,815	£39,506
Incremental FH effect (change compared with base value)	100%	70–300%	£13,605	£58,308
GH dose	0.23 mg/kg/week	0.175–0.7 mg/kg/week	£12,686	£121,341
GH cost	£20.82	£15.25–25	£29,577	£48,887
Annual rate of discounting for benefits	1.5%	0–6%	£39,609	£44,656
Annual rate of discounting for costs	6%	0–12%	£35,784	£46,540
ICER	£40,815		£10,873	£121,341
Two-way sensitivity analysis				
GH dose	0.23 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	70–300%	£4,229	£173,344
Length of treatment	5 years	1–13 years		
FH effect	100%	70–300%	£3,624	£83,238

Base case 2

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	5 years	1–13 years	£22,622	£121,745
Continuance of treatment	100%	30–100%	£85,368	£83,535
Incremental FH effect (change compared with base value)	100%	70–300%	£28,456	£121,954
GH dose	0.35 mg/kg/week	0.175–0.7 mg/kg/week	£17,760	£169,877
GH cost	£20.82	£15.25–25	£61,744	£102,334
Annual rate of discounting for benefits	1.5%	0–6%	£82,845	£93,400
Annual rate of discounting for costs	6%	0–12%	£74,820	£97,368
ICER	£85,368		£17,760	£169,877
Two-way sensitivity analysis				
GH dose	0.35 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	70–300%	£5,920	£242,681
Length of treatment	5 years	1–13 years		
FH effect	100%	70–300%	£7,541	£173,922

PWS *contd*

Base case 3

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	8 years	1–13 years	£1,466	£7,858
Continuance of treatment	100%	30–100%	£7,030	£6,753
Incremental FH effect (change compared with base value)	100%	70–300%	£2,343	£10,043
GH dose	0.0333	0.025–0.1 mg/kg/day	£2,186	£20,897
GH cost	£20.82	£15.25–25	£5,095	£8,420
Annual rate of discounting for benefits	1.5%	0–6%	£6,672	£8,203
Annual rate of discounting for costs	6%	0–12%	£5,572	£8,925
ICER	£7,030		£1,466	£20,897
Two-way sensitivity analysis				
Drug dose		0.025–0.1 mg/kg/day		
FH effect		70–300%	£729	£29,853
Length of treatment		1–13 years		
FH effect		70–300%	£489	£11,225

ISS

Base case 1

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	6 years	1–13 years	£4,295	£16,735
Continuance of treatment	71%	30–100%	£14,478	£13,290
Incremental FH effect (change compared with base value)	100%	10–240%	£5,624	£134,978
GH dose	0.35 mg/kg/week	0.175–0.7 mg/kg/week	£6,854	£26,785
GH cost	£20.82	£15.25–25	£9,783	£16,166
Annual rate of discounting for benefits	6%	0–6%	£13,002	£15,092
Annual rate of discounting for costs	1.5%	0–12%	£11,550	£15,816
ICER	£13,498		£4,295	£134,978
Two-way sensitivity analysis				
GH dose	0.35 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	10–240%	£2,856	£267,854
Length of treatment	6 years	1–13 years		
FH effect	100%	10–240%	£1,790	£167,351

Base case 2

Parameter	Base case value	Range in sensitivity analysis	Minimum ICER	Maximum ICER
One-way sensitivity analysis				
Length of treatment	7 years	1–13 years	£8,096	£31,503
Continuance of treatment	71%	30–100%	£28,761	£26,871
Incremental FH effect (change compared with base value)	100%	10–240%	£11,334	£272,019
GH dose	0.23 mg/kg/week	0.175–0.7 mg/kg/week	£20,582	£80,397
GH cost	£20.82	£15.25–25	£19,778	£32,534
Annual rate of discounting for benefits	6%	0–6%	£26,008	£31,074
Annual rate of discounting for costs	1.5%	0–12%	£22,526	£33,017
ICER	£27,202		£8,096	£272,019
Two-way sensitivity analysis				
GH dose	0.23 mg/kg/week	0.175–0.7 mg/kg/week		
FH effect	100%	10–240%	£8,576	£803,973
Length of treatment	7 years	1–13 years		
FH effect	100%	10–240%	£3,373	£315,027

Appendix 11

Summary of evidence of effectiveness of GH in GHD: RCT

Reference and design	Intervention	Patients	Outcome measures
Soliman & Abdul-Khadir, 1996[23] (Egypt) Study type/design: RCT after determination of GH status Jadad score: 2/5	***Treatment arms*** Group I: GHD Ia. GH, 30 U/m^2/week Ib. GH, 15 U/m^2/week Group II: partial GHD IIa. GH, 15 U/m^2/week IIb. Control (IIIa and IIIb, see appendix 19) Length of treatment: 1 year Other interventions used: not stated	Total number: 77 patients Ia. GH, 30 U/m^2: 20 patients Ib. GH, 15 U/m^2: 14 patients IIa. GH, 15 U/m^2: 9 patients IIb. Control: 10 patients (IIIa and IIIb: 24 patients) Characteristics of target population: • < 3rd percentile in height • Prepubertal • Peak GH response to clonidine and insulin provocation was < 7 µg/l in Group I, 7–10 µg/l in Group II Participants: • Mean age ± SD (years): Group I, 7.3 ± 1.8; Group II, 6.8 ± 2.1 • GV ± SD (cm/year): Group I, 3.7 ± 1.2; Group II, 3.9 ± 1.1 • HtSDS ± SD: Group I, 3.2 ± 1.2; Group II, 2.8 ± 1.0 • BA < 10 years Setting: outpatient clinic	Height HtSDS GV (cm/year) Circulating IGF-I, GH, thyroxine and TSH concentrations Oral glucose tolerance Length of follow-up: 0.96–1.04 years

Results (mean ± SD)

- HtSDS before treatment: Group Ia, –3.3 ± 1.2; Group Ib, –2.85 ± 1.2; Group IIa, –3.4 ± 0.8; Group IIb, –3.1 ± 0.6
- HtSDS after treatment: Group Ia, –2.46 ± 1.26; Group Ib, –1.12 ± 1.16; Group IIa, –2.3 ± 0.45; Group IIb, –2.8 ± 0.45 ($p < 0.05$ before and after for Groups Ia, Ib and IIa; $p < 0.05$ for Group IIa vs IIb)
- GV (cm/year) before treatment: Group Ia, 3.45 ± 1.23; Group Ib, 3.44 ± 1.27; Group IIa, 3.65 ± 1.1; Group IIb, 4.3 ± 1.0
- GV (cm/year) after treatment: Group Ia, 9.11 ± 2.25; Group Ib, 8.1 ± 1.52; Group IIa, 8.4 ± 1.4; Group IIb, 5.7 ± 1.8 ($p < 0.05$ before and after for Groups Ia, Ib and IIa; $p < 0.05$ for Group IIa vs IIb)
- Positive responders (GV ≥ 2 cm/year above pretreatment GV): Group Ia, 20/20; Group Ib, 10/10; Group IIa, 8/9; Group IIb, 9/12
- No adverse effects reported

Comments

Methodological comments

- Allocation to treatment groups: Random, method not stated
- Blinding: Not stated
- Comparability of treatment groups: No differences in baseline GV and HtSDS of patients and controls
- Method of data analysis: Not ITT analysis. Data presented as mean ± SD. Paired Student's *t*-test used to analyse changes in each group before treatment and after 1 year. Simple linear regression was used to test correlation between variables. No point estimates with CIs given
- Sample size/power calculation: Not stated
- Attrition/drop-out: Four children in Group Ib were excluded from the study because of lack of compliance

General comments

- Generalisability: Inclusion and exclusion criteria defined. Exclusion criteria: reduced weight to height; systemic disease; history of head trauma or cranial irradiation; malnutrition; psychosocial dwarfism or hypothyroidism
- Outcome measures: Appropriate outcome measures used. HtSDS calculated as (X1–X2) ÷ SD, where X2 and SD are age-matched population mean height and SD, and X1 is the patient height. Normal population data according to Tanner
- Complicated design of study. Drop-outs/withdrawals reported
- Conflict of interests: Not stated

continued

Quality assessment for RCTs (Jadad score)	
Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 4/77 (5%) Group Ib: 4/14 (28.6%) Total GH drop-outs: 4/43 (9.3%) Total control drop-outs: 0/10 (0%)

TSH, thyroid-stimulating hormone

Appendix 12

Summary of evidence of effectiveness of GH in GHD: non-RCTs reporting final height

Reference and design	Intervention	Patients	Outcome measures
Cutfield *et al.*, 1999[44] (International) Single cohort extracted from database	Median of mean GH doses: 0.49 IU/kg/week Median of mean injection frequency: 5.2/week Median treatment duration: 8.1 years ***Swedish subgroup*** Median of mean GH dose (IU/kg/week): 0.65 at start, 0.67 at finish Median of mean injection frequency: 7.0/week at start, 6.8/week at finish Median treatment duration: 9.4 years	369 patients in database met inclusion criteria: • Idiopathic GHD (peak GH concentration < 10 µg/l following provocation) • At FH (see criteria below) • > 2 years GH treatment prior to puberty • > 5 years total GH treatment Other characteristics: • Median age at start: 9.8 years • Median age at finish: 18.4 years • 73% male, 75% Caucasian, 25% Asian • 40% received pituitary GH • 65% received < 5 injections/week for 40% of treatment duration • 22% stopped treatment before FH reached Subgroup of Swedish patients with current conventional GH treatment throughout (n = 69): • Median age at start: 8.4 years • Median age at finish: 18.5 years • Sex ratio (male:female): 1.7	FH (cm and SDS) Final minus mid-parental HtSDS Final minus starting HtSDS

Results (medians and 10th–90th percentile)

Total cohort

- Pretreatment HtSDS: –3.1 (–4.7 to –2.0)
- Final HtSDS: –1.5 (–3.1 to 0.2)
- Final minus mid-parental HtSDS: –0.5 (–2.3 to 0.7)
- Factors related to FH (all $p < 0.005$): mid-parental HtSDS ($r = 0.62$), GH dose frequency ($r = 0.37$), GH treatment duration ($r = 0.28$), peak stimulated GH concentration ($r = –0.25$), age ($r = –0.19$), GVSDS over first year of GH ($r = 0.20$)

Swedish subgroup

- Pretreatment HtSDS: –2.6 (–4.2 to –1.5)
- Final HtSDS: –0.32 (–1.46 to 1.3)
- Final minus mid-parental HtSDS: 0.03 (–1.28 to 1.16)
- Adverse effects: No discussion

FH criteria: GV < 2 cm/year calculated over a minimum of 9 months; CA > 17 years or BA > 16 years in boys; CA > 15 years or BA > 14 years in girls
Height SDS and GV determined from growth charts of Tanner
BA estimated according to methods of Greulich and Pyle

Comments

Methodological comments

- Patients chosen according to inclusion criteria, but no treatment groups
- Method of data analysis: No within-group before and after treatment statistical comparisons
- Sample size/power calculation: No discussion

General comments

- Generalisability: Patients appeared to be representative of idiopathic GHD, but did not include children with non-idiopathic GHD
- Outcome measures: Measures seem appropriate, but not all reported (e.g. FH in cm)
- Intercentre variability: No assessment
- Conflict of interests: Authors writing on behalf of KIGS international board

continued

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	
Proper sampling		✗				
Adequate sample size	✗					However, no before/after comparisons
Objective outcomes	✗					But not all reported
Blind assessment			✗			
Objective eligibility criteria	✗					
Reported attrition					✗	
Comparability of groups					✗	
Generalisability		✗				

Reference and design	Intervention	Patients	Outcome measures
August *et al.*, 1998[45] (USA) Single cohort extracted from database	GH: no dose information Average duration deduced from starting and ending ages: approximately 4.5 years	Boys: 480 Girls: 194 ***Boys*** CA: 12.7 ± 2.2 years at enrolment 17.3 ± 1.0 years at NAH Target HtSDS: –0.4 ± 0.8 ***Girls*** CA: 11.2 ± 2.1 years at enrolment 15.6 ± 1.5 years at NAH Target HtSDS: –0.5 ± 0.7 Inclusion criteria: • Idiopathic GHD (maximum stimulated GH level ≤ 10 µg/l and no evidence of organic cause) • Prepubertal on enrolment in NCGS • Spontaneous onset of puberty (appearance of Tanner stage II breast development in girls or testicular volume of ≥ 3 ml in boys) • Available NAH • No treatment with glucocorticoids, sex steroids, or agents to alter or delay puberty	HtSDS

Results (mean ± SD)
- Boys: HtSDS, –2.6 ± 0.8 at enrolment, –1.3 ± 1.0 at NAH
- Girls: HtSDS, –3.0 ± 0.9 at enrolment, –1.6 ± 0.9 at NAH
- Significant decrease in HtSDS deficit during puberty ($p < 0.0001$)
- Age at onset of puberty was negatively correlated with total height gained during puberty and the percentage of final adult height gained during puberty
- Adverse effects: No mention

Comments

Methodological comments
- Single cohort selected from database on basis of inclusion criteria
- Possible sample biases
- HtSDS unclearly reported – appears to be median. No before/after analyses reported
- Attrition/drop-out: Retrospective

General comments
- Generalisability: May not generalise to children with different aetiology of GHD or who start treatment earlier
- Outcome measures: NAH compared with 18-year-olds may underestimate effect because participants averaged < 18 years of age
- Conflict of interests: Support from Genentech

Enrolment HtSDS derived from published standards for North American children and adults

NAH SDS relative to mean heights of normal 18-year-olds

Subgroup of patients met more strict NAH criteria, as above, plus a BA criterion (BA ≥ 16 years for boys and ≥ 14 years for girls). However, starting and ending heights in this subgroup did not differ from the overall group

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	
Proper sampling		✗				
Adequate sample size	✗					However, no before/ after comparisons
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria	✗					
Reported attrition					✗	
Comparability of groups					✗	
Generalisability		✗				

Appendix 13

Summary of evidence of effectiveness of GH in TS: RCTs

Reference and design	Intervention	Patients	Outcome measures
CGHAC, 1998[24] (abstract only) (Canada) RCT: GH vs control (no treatment) Jadad score: 2/5	GH: 0.05 mg/kg six times weekly (Humatrope) All received oestrogen/ progesterone treatment starting at age 13 years	*n* = 154 69 achieved FH and formed basis of this report Age range at start: 7–13 years GH group: 40 patients Control group: 29 patients Randomly assigned (stratified for height relative to age at entry) Setting: not specified	FH Height change from baseline

Results (mean ± SD)

- FH: GH group, 146.2 ± 6.5 cm; control group, 141.4 ± 4.7 cm
- Height change from baseline: GH group, 24.6 ± 7.8 cm; control group, 17.0 ± 4.7 cm
- Change in HtSDS (based on Lyon *et al.*, 1985)[7] from baseline: GH group, 1.5 ± 0.5; control group, 0.3 ± 0.4
- Mean GH effects estimated by ANCOVA: FH, 6.5 ± 1.1 cm ($p < 0.001$); change in height from baseline, 7.9 ± 1.7 cm ($p < 0.001$); change in HtSDS from baseline, 1.2 ± 0.1 ($p < 0.001$)

Comments

Methodological comments

- Allocation to treatment groups: Randomised (stratified), but method not described
- Blinding: No information
- Comparability of treatment groups: No information. Given results are from a subset of initially randomised groups; comparability may be compromised
- Method of data analysis: Hypothesis tests, and no CIs given. Covariates in ANCOVA not specified
- Sample size/power calculation: None
- Attrition/drop-out: 29% of initial patient population dropped out (45 patients)

General comments

- Generalisability: Little information, but seem representative of target population
- Outcome measures: FH appropriate; height prediction methods questioned
- Intercentre variability: Not assessed
- Conflict of interests: No information

FH criteria: Growth rate < 2 cm/year and BA ≥ 14 years

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Total: 29% Treated drop-outs: 13/76 (17%) Untreated drop-outs: 32/79 (41%)

Reference and design	Intervention	Patients	Outcome measures
Rosenfeld, 1990[25] and 1989[26] (USA) RCT Jadad score: 2/5 (No treatment group for year 1 only; results beyond year 1 not reported)	Met-hGH: 0.125 mg/kg 3 x/week intramuscular for 12–20 months Control: no treatment • OX, 0.125 mg/kg/day • Combination OX and GH, doses as above	*n* = 71 Age: 9.3 years (range, 4.7–12.4 years) GH group: 17 patients GV: 4.5 ± 0.8 cm/year GVSDS: 0.5 ± 0.8 Control group: 18 patients GV: 4.2 ± 1.1 cm/year GVSDS: 0.2 ± 1.2 OX group: 19 patients GV: 4.1 ± 1.9 cm/year GVSDS: 0.2 ± 1.0 GH + OX group: 17 patients GV: 4.3 ± 0.9 cm/year GVSDS: 0.2 ± 0.9 • Height ≥ 1 SD below mean for age • Pretreatment growth rate < 6 cm/year • Normal thyroid function • Provocative serum GH ≥ 7 ng/ml Setting: not specified	GV GVSDS for TS (Ranke)

Results (mean ± SD)

- GV: GH group, 6.6 ± 1.2 cm/year; control group, 3.8 ± 1.1 cm/year; OX group, 7.6 ± 1.5 cm/year; OX + GH group, 9.8 ± 1.4 cm/year
- GVSDS: GH group, +3.1 ± 1.2; control group, –0.1 ± 1.0; OX group, +4.4 ± 1.8; OX + GH group, +6.6 ± 1.2
- Adverse effects: None discussed

Comments

Methodological comments

- Allocation to treatment groups: Randomised, but method not discussed
- Blinding: No information
- Comparability of treatment groups: Comparable in pretreatment growth. Other variables not compared
- Method of data analysis: No statistical comparisons between groups
- Attrition/drop-out: Three patients withdrawn within first 12 months

General comments

- Generalisability: Patients appear representative of target group
- Outcome measures: GV and TS-standardised GV are appropriate
- Intercentre variability: Not assessed
- Conflict of interests: Support from Genentech

GVSDS based on TS standard (Ranke)

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	
Was there a description of withdrawals and drop-outs?	1 (results table suggests no drop-out in year 1, but not stated in text)
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	0%

Reference and design	Intervention	Patients	Outcome measures
Rovet & Holland, 1993[13] (Canada) Preliminary report from Canadian long-term multicentre RCT Jadad score: 2/5	GH: 0.05 mg/kg s.c. 6 evenings/week Maximum weekly dose of 15 mg (Humatrope) No treatment Length of treatment: 18 months Other interventions: none reported for this subgroup	122 patients enrolled 95 participating at time of evaluation (51 received GH; 44 no treatment) 86 compliant 65 available for evaluation at 18 months 48 in analysis (28 on GH; 20 no treatment) • TS (included Y mosaic forms, provided gonadal remnants removed) • Normal GH secretion • Age range, 7–12 years, 11 months • Height ≤ 10th percentile on TS chart • Documented height velocity for previous 6 months • Normal fasting serum glucose • Endogenous GH ≥ 8 µg/l on provocative physiological testing Baseline characteristics of 95 patients participating: • Age: GH group, 10.8 ± 0.2 years; no treatment group, 10.7 ± 0.2 years • BA: GH group, 9.0 ± 0.2 years; no treatment group, 8.8 ± 0.2 years • Height: GH group, 121.0 ± 1.2 cm; no treatment group, 120.1 ± 1.1 cm Exclusion criteria: • Coincident disease likely to influence growth • Previous radiation to CNS/spinal axis • Previous treatment with adrenal androgens, oestrogen or GH • Untreated hypothyroidism • Started oestrogen treatment (in current trial)	• Piers Harris self-concept test (child self-report) • Achenbach's Child Behaviour Checklist (completed by parents) • Youth Self-Report (child) • GV

Results (mean ± SD)

At 18 months – child self-ratings of self-concept:
- Global: GH group, 76.5 ± 18.9; no treatment group, 64.4 ± 21.7 ($p = 0.001$)
- Appearance: GH group, 67.0 ± 24.5; no treatment group, 55.7 ± 24.9 ($p = 0.08$)
- Intelligence: GH group, 75.0 ± 23.8; no treatment group, 56.2 ± 25.2 ($p = 0.01$)
- Peer relations: GH group, 66.4 ± 27.4; no treatment group, 32.4 ± 25.6 ($p = 0.001$)

At 18 months – parent's ratings:
- Friendships: GH group, 3.15 ± 0.6; no treatment, group, 2.72 ± 0.83 ($p = 0.05$)
- Popularity: GH group, 66.4 ± 27.4; no treatment group, 32.4 ± 25.6 ($p = 0.001$)
- Teasing: GH group, 0.69 ± 0.55; no treatment group, 1.05 ± 0.61 ($p = 0.05$)
- Hyperactivity: GH group, 59.6 ± 7.6; no treatment group, 65.2 ± 8.0 ($p = 0.05$)
- Decreased mathematics performance over time in GH group but not in no treatment group (significant group-by-session interaction, $p < 001$)

GV: In GH group, GH was significantly greater than baseline at all evaluations; no statistical comparison reported

Correlations with GV: Large growth rate was associated with fewer somatic complaints ($p < 0.01$), less hyperactivity ($p < 0.01$), more friends ($p < 0.05$), better social competence ($p < 0.05$), greater popularity ($p < 0.01$), less teasing ($p < 0.05$), improved perceived physical appearance ($p < 0.05$) and improved perceived intelligence ($p < 0.01$)

Drop-outs were significantly more likely to be: from single parent families or families with greater protectiveness and dysfunctional ratings. Children from families dropping out were rated significantly lower in initial social competence and had more behavioural problems

Comments

Methodological comments
- Allocation to treatment groups: Method of randomisation not reported
- Blinding: None reported
- Comparability of treatment groups: Baseline comparability of groups still participating was reported, but the comparability of subgroups as analysed groups was not reported
- Method of data analysis: Analysis not on an ITT basis. Point estimates and CI of differences were not reported. Significance levels estimated using ANOVA. No corrections for multiple comparisons
- Sample size/power calculations: No power calculations
- Attrition/drop-out: 49% drop-out rate from those still participating in trial

continued

***Comments* contd**

General comments

- Generalisability: Inclusion and exclusion criteria were defined. Analysis limited to 48 out of 95 patients participating in trial (51%) who had been followed for 18 months. Therefore, results may not be representative
- Outcome measures: Limited to psychological intervention only, with subjective ratings by child and parents in unblinded study. No objective confirmation of reports. Study not blinded, so cannot exclude differing input into those patients on active compared with no treatment (whether from parents/researchers). Short-term outcomes (18 months of treatment). Drop-out analysis apparently based on 65 participants, among whom the drop-out rate was considerably greater in treated than untreated patients. This could bias results, although evaluation of drop-outs from the final analysis appears not to have been conducted
- Intercentre variability: Not assessed (13 sites)
- Conflict of interests: Support from Eli Lilly, Canada

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 (no method)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Percentage of patients who were not available for evaluation at 18 months (differs from those analysed – see table below): Overall: 32% (30/95) GH group: 39% (20/51) Control group: 23% (10/44) Drop-out rate from analysis of those available for evaluation: Overall: 26% (17/65) GH group: 10% (3/31) Untreated group: 41% (14/34)

Patient status	Number of patients		
	GH-treated	Untreated	Total
Enrolled			122
Participating at 18 months	51	44	95
Available at 18 months	31	34	65
In analysis	28	20	48

Reference and design	Intervention	Patients	Outcome measures
Ross et al., 1997[27] (USA) Part of long-term double-blind, placebo-controlled RCT Jadad score: 2/5	GH, 0.1 mg/kg thrice weekly by s.c. injection (Humatrope) Placebo Length of treatment: 1–7 years (GH, 3.1 ± 1.4 years; placebo, 2.5 ± 1.5 years) Other interventions: none specified	40 girls 20 received GH 20 received placebo • TS • Age: 5–11.9 years at entry (GH group, 9.9 ± 2.2 years; placebo group, 9.3 ± 1.8 years) Exclusion criteria: • Oestrogen treatment • Earlier treatment with androgens • Verbal IQ < 70 Setting: testing in hospital/NIH	Primary outcome measures were neuro-cognitive evaluations (20 tests total): • General cognitive abilities • Academic achievement • Memory (verbal and non-verbal) • Language • Visual-spatial/ perceptual • Visual-motor/ perceptual • Attention/impulsivity • Affect recognition

Results (mean ± SD)

- After Bonferroni correction, no GH vs placebo comparisons were significant
- Delayed recall of Rey Complex figure reached traditional significance, with GH-treated girls performing better than placebo-treated girls (21 ± 11 vs 15 ± 8, $p < 0.05$)
- Adverse effects: Not reported

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported. No details of how sample was selected from those in ongoing study
- Blinding: Reported as double-blind, but no details of methods used to ensure blinding, and it was not stated who was blinded
- Comparability of treatment groups: Groups reported as comparable at baseline on age, duration of treatment, race, karyotype and socio-economic status
- Method of data analysis: Hypothesis tests (two-tailed with Bonferroni correction for multiple comparisons)
- Sample size/power calculations: No power calculations
- Attrition/drop-out: No mention of drop-outs

General comments

- Generalisability: Inclusion and exclusion criteria were defined. Not clear how this subset of 40 patients was selected from those participating in the larger trial
- Outcome measures: This report was limited to cognitive function. Girls treated for varying lengths of time
- Intercentre variability: Not assessed – testing at one centre
- Conflict of interests: Funding support from NIH grant and Eli Lily and Company

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	1
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	None reported

s.c., subcutaneous; ITT, intention to treat; ANOVA, analysis of variance; NIH, National Institutes of Health

Appendix 14

Summary of evidence of effectiveness of GH in TS: non-RCTs reporting final height

Reference and design	Intervention	Patients	Outcome measures
Dacou-Voutetakis *et al.*, 1998[46] (Greece) Non-randomised GH/control (no treatment) (No treatment due to refusal of treatment or lack of GH available)	GH: mean dose 0.78 ± 1.2 IU/kg/week s.c. injections 5–7 times/week All received oestrogen therapy	*n* = 123 GH: 82 patients No treatment: 41 patients ***Followed to FH*** Treatment group: 35 patients Age: 12.0 ± 1.8 years BA: 10.2 ± 2.1 years HtSDS: +0.47 ± 0.9 GV: 4.0 ± 1.5 cm/year Target height: 158.3 ± 5.2 cm Age at oestrogen administration: 15.6 ± 1.3 years Mean duration of GH: 2.7 ± 1.2 years No treatment group: 27 patients Age: 12.4 ± 3.3 years BA: not reported HtSDS: +0.31 ± 1.1 GV: 4.0 ± 2.1 cm/year Target height: 156.3 ± 6.2 cm Age at oestrogen administration: 14.2 ± 1.8 years TS confirmed by karyotype Setting: single children's hospital	FH Final HtSDS (Ranke TS standard) Target height Projected height BA (Greulich and Pyle)

Results (mean ± SD)

- FH: GH group, 146.1 ± 6.6 cm; no treatment group, 144.0 ± 6.1 cm (NS)
- Final HtSDS: GH group, +0.24 ± 1.0; no treatment group, +0.07 ± 0.9 (NS)
- ΔTarget height minus FH: GH group, 12.6 ± 4.9 cm; no treatment group, 9.8 ± 6.8 cm (NS)
- Projected height: GH group, 145.0 ± 9.8 cm; no treatment group, 143.3 ± 7.4 cm (NS)
- In GH group: Final HtSDS positively correlated with HtSDS at baseline ($r = 0.73$, $p = 0.001$) and with BA at baseline ($r = 0.64$, $p = 0.001$). Final HtSDS also positively related to maternal height ($r = 0.57$, $p = 0.01$), target height ($r = 0.66$, $p = 0.001$) and birth weight ($r = 0.54$, $p = 0.01$)
- 37% of GH group and 18% of no treatment group reached FH ≥ 150 cm (NS)
- BA was not discussed
- Adverse effects: No mention

Comments

Methodological comments

- Allocation to treatment groups: Self-selection or lack of drug availability
- Blinding: Open treatment
- Comparability of treatment groups: Groups appear comparable, with the exception of the time of initiation of oestrogen therapy. Treatment group was significantly older than no treatment group at oestrogen initiation (15.5 vs 13.9 years, respectively)
- Sample size/power calculation: None mentioned
- Attrition/drop-out: No mention; however, results table suggests no drop-outs
- FH definition: Epiphyses closed on radiographic film of hand and wrist, and the annual GV was less than 1 cm
- Target height = [(maternal height + paternal height) ÷ 2] – 6.5 cm

continued

***Comments* contd**

General comments

- Generalisability: Patients seem appropriate, although perhaps older than the usual age of initiation of GH treatment and of oestrogen therapy, particularly in GH group
- Outcome measures: Generally appropriate. No mention of how projected height was computed
- Intercentre variability: Single centre
- Conflict of interests: Pharmacia Sweden donated rhGH in initial phase of study

SDS based on TS standard (Ranke)

Short-term results not reported because other short-term results available from studies of higher quality

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Non-randomised
Proper sampling			✗			Neither random nor consecutive sample
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria				✗		
Reported attrition				✗		Results table suggests no drop-outs
Comparability of groups	✗					
Generalisability		✗				

Reference and design	Intervention	Patients	Outcome measures
Hochberg & Zadik, 1999[47] (Israel) Two centres Open, non-randomised GH/control (no treatment) (No treatment due to refusal to participate)	GH: 8.2 mg/m^2/week in daily s.c. injections (BioTropin and Humatrope) Therapy continued for 5.1 ± 1.9 years until commencement of BA of 14 years Oestrogen therapy added 2 years or more after GH initiation (CA ≥ 12 years)	*n* = 49 GH group: 25 patients Age: 10.7 ± 1.4 years BA: 9.3 ± 1.0 years HtSDS (Turner standard): –0.5 ± 1.3 HtSDS (TW standard): –2.4 ± 1.1 GVSDS (TW standard): –2.1 ± 0.4 Projected height: 142.6 ± 5.2 cm Target height: 163.3 ± 4.8 cm Control group: 24 patients Age: 10.7 ± 1.4 years BA: 9.4 ± 0.9 years HtSDS (Turner standard): –0.2 ± 1.5 HtSDS (TW standard): –2.2 ± 1.4 GVSDS ± TW standard): –2.1 ± 0.5 Projected height: 143.5 ± 4.2 cm Target height: 163.5 ± 5.8 cm Inclusion criteria: • TS by karyotype (four karyotypes) • Age: 7–14 years • BA: < 12 years Setting: two centres	FH (cm) Height gain over projection Height deficit

Results (mean ± SD)

- FH: GH group, 147.3 ± 4.9 cm; no treatment group, 142.9 ± 5.1 cm
- Height gain (FH minus projected height): GH group, 4.7 ± 2.9 cm; no treatment group, –0.6 ± 2.2 cm ($p < 0.005$)
- Height deficit: GH group, 16.0 ± 4.6 cm; no treatment group, 20.7 ± 6.0 cm ($p < 0.01$)
- Significant correlation between FH and target height in GH group ($r = 0.553$, $p < 0.005$) (and to mother and father's heights separately), but not in no treatment group ($r = 0.383$, $p = 0.065$)
- Adverse effects: There were "no clinically apparent untoward effects". Hyperinsulinaemia with normal glucose tolerance was observed in most patients in whom it was tested

Comments

Methodological comments

- Allocation to treatment groups: Self (parent)-selection
- Blinding: Open study
- Comparability of treatment groups: No apparent differences in groups
- Method of data analysis: Hypothesis tests used, but no CIs given
- Sample size/power calculation: No power estimates, although stated that *n* was determined to allow sufficient power for comparisons
- Attrition/drop-out: One patient

General comments

- Generalisability: Patients seem representative of target population
- Outcome measures: Measures seem appropriate, although FHs not expressed in SDS
- Intercentre variability: Not assessed
- Conflict of interests: Eli Lilly, Israel, and Biotechnology General, Israel, supplied some GH for some patients for part of the study

FH defined as height measurement taken 2 years or more after GV declined below 2 cm/year and after a BA of 15 years was repeated
Heights expressed as SDS of the general population from Tanner growth charts and Ranke's Turner growth charts
Ranke TS growth charts used for adult height projection
Height gain = FH – projected height
Height deficit = target height – FH

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Non-randomised
Proper sampling			✗			Neither random nor consecutive sample
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria	✗					
Reported attrition		✗				Results from 49 of 50 patients who started trial
Comparability of groups	✗					
Generalisability	✗					

Reference and design	Intervention	Patients	Outcome measures
Pasquino *et al.*, 1996[48] (Italy) Retrospective, non-randomised GH/control (no treatment)	GH: 0.5 IU/kg/week in year 1 and 1 IU/kg/week subsequently, 6 days/week Oestrogen/progesterone treatment in girls without spontaneous puberty Treated for 3–6 years, with mean duration of 4.5 ± 0.9 years	Original cohort of 32 GH-treated patients: 18 attained FH Age: 13.0 ± 2.0 years BA: 11.1 ± 1.4 years HtSDS (Lyon): 0.7 ± 0.9 HtSDS (Italian): 0.1 ± 1.0 26 untreated patients attained FH: 18 matched patients served as controls Age: 12.8 ± 1.6 years BA: 11.6 ± 1.2 years HtSDS (Lyon): 0.8 ± 0.7 HtSDS (Italian): 0.3 ± 0.7 Prepubertal at start of treatment Euthyroid Without relevant cardiac or renal abnormalities Controls matched for age, BA and karyotype Setting: not specified	Final HtSDS Change in HtSDS during therapy Change in height compared between matched pairs of girls FH minus projected height

Results (mean ± SD)

- Final HtSDS (Lyon): GH group, 1.0 ± 1.6; no treatment group, –0.2 ± 1.1 ($p < 0.05$)
- Final HtSDS (Italian TS standard): GH group, 0.9 ± 1.2; no treatment group, 0.04 ± 0.8 ($p < 0.05$)
- Change in HtSDS for matched pairs (Lyon): GH group, 0.3 ± 1.1; no treatment group, –1.0 ± 0.8 ($p < 0.001$)
- Change in HtSDS for matched pairs (Italian standard): GH group, 0.8 ± 0.7; no treatment group, –0.3 ± 0.5 ($p < 0.001$)
- Final height (Italian cross-sectional standards): GH group, 147.6 ± 7.3 cm; no treatment group, 142.2 ± 4.9 cm
- FH minus projected height: GH group, –1.1 ± 4.8 cm; no treatment group, –6.2 ± 3.9 cm ($p < 0.01$)
- Positive correlation ($r = 0.56$, $p < 0.05$) between target height and FH in treated GH group
- Positive correlation ($r = 0.56$, $p < 0.05$ [Lyon]; $r = 0.58$, $p < 0.05$ [Italian standard]) between height gain in SDS and age at start of GH treatment
- Adverse effects: "No side-effects, or relevant metabolic alterations were observed during rhGH treatment"

Comments

Methodological comments

- Allocation to treatment groups: Non-randomised
- Blinding: Open treatment
- Comparability of treatment groups: Controls matched to treated patients; no substantial differences, although seemingly no test for GH secretion in control patients
- Method of data analysis: Hypothesis tests but no CIs
- Sample size/power calculation: None computed
- Attrition/drop-out: None reported (retrospective)

General comments

- Generalisability: Little information given, but patients would appear to be representative of target population
- Outcome measures: Outcomes seem appropriate, although little explanation of comparison of heights in matched pairs
- Intercentre variability: Unclear whether study was multicentre or single centre
- Conflict of interests: No mention
- Correlations should be considered with caution as populations were relatively small

FH criteria: Observation for at least 1 year without any growth above 0.5 cm after discontinuation of treatment

HtSDS evaluated using Lyon standards for TS and unpublished SDS for Italian girls with TS from multicentre study

Mid-parental target height calculated as described by Tanner

Unclear whether study was prospective or retrospective

Quality assessment (revised from Spitzer et al., 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Non-randomised
Proper sampling			✗			Neither random nor consecutive sample
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria				✗		
Reported attrition		✗				Results table suggests no loss
Comparability of groups	✗					
Generalisability	✗					

Reference and design	Intervention	Patients	Outcome measures
Taback *et al.*, 1996[49] (Canada) Retrospective, non-randomised treatment/no treatment (based on parent request to treat)	GH: 0.05 mg/kg/day s.c. 6 days/week (maximum 15 mg/week) (Protropin, Humatrope) Continued until height velocity < 1 cm/6 months All received oestrogen – timing decided on case-by-case basis Average GH duration: 3.6 years	*n* = 31 GH group: 17 patients Median age: 10.2 years (range, 4.2–11.8 years) Median HtSDS: 0.5 (range, –1.7 to 1.4) Median predicted height: 148.2 cm (range, 131.5–155 cm) No treatment group: 14 patients Median age: 10.3 years (range, 3.3–11.8 years) Median HtSDS: –0.1 (range, 23.2–1.8) Median predicted height: 144.0 cm (range, 120.2–158.0 cm) TS confirmed by karyotype Height measured in a growth clinic between ages 3 and 12 years, and until adult height attained Exclusion criteria: • Anabolic steroids for longer than 12 months, presence of a Y-containing cell line, enrolment in Canadian randomised controlled trial Setting: not specified	FH Difference between final and projected height

Results

- FH (median): GH group, 148.0 cm; no treatment group, 140.7 cm (p = 0.004)
- Comparison of distribution of individual differences between attained and projected heights revealed higher values in the GH group (p = 0.034)
- Adverse effects: "no major side-effects attributable to GH were noted"

Comments

Methodological comments

- Allocation to treatment groups: Self (parent)-selection
- Blinding: Open
- Comparability of treatment groups: GH group taller (0.6 SD) and had greater PAH at initiation (4.2 cm). Also, GH group received oestrogen–progesterone about 1 year later than no treatment group
- Method of data analysis: Hypothesis tests, but no CIs
- Sample size/power calculation: No power estimates
- Attrition/drop-out: Retrospective

General comments

- Generalisability: Patients seem representative of target population
- Outcome measures: FH is appropriate, no HtSDS
- Intercentre variability: Not assessed
- Conflict of interests: First author received Eli Lilly Canada Inc. clinical and research fellowship

Adult height defined as tallest height measured at a growth clinic after height velocity had decreased to 1 cm or less over 6 months

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Self-selected into trial or not
Proper sampling sample			✗			Neither random nor consecutive
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria					✗	Retrospective
Reported attrition					✗	Retrospective
Comparability of groups			✗			Control group taller at baseline
Generalisability	✗					

rhGH, recombinant human GH; TW, Tanner–Whitehouse (standard based on normal population)

Appendix 15

Summary of evidence of effectiveness of GH in CRF: RCTs

Reference and design	Intervention	Patients	Outcome measures
Fine *et al.*, 1994[28] (USA) RCT Jadad score: 2/5	GH vs placebo GH, 0.05 mg/kg/day s.c. (Nutropin), or placebo in equivalent volume (dose adjusted every 3 months) 2 years	GH group: 82 patients 21 girls, 61 boys Age: 6.0 ± 3.9 years Height age: 4.0 ± 2.9 years BA: 4.2 ± 3.0 years HtSDS: –2.9 ± 0.9 Placebo group: 43 patients 14 girls, 28 boys Age: 5.7 ± 3.6 years Height age: 3.8 ± 2.8 years BA: 4.2 ± 2.9 years HtSDS: –2.9 ± 1.0 Inclusion criteria: • Irreversible renal insufficiency • Creatinine clearance > 5 and < 75 ml/minute/1.73 m^2 • Height < 3rd percentile for CA • BA < 10 years for girls and < 11 years for boys • Prepubertal status (Tanner stage I) Setting: multicentre	GV HtSDS Height age BA Cumulative Δheight age minus ΔBA Weight gain TSF thickness MAMC

Results

- GV (mean ± SD) (GH vs placebo):
  Year 1: 10.7 ± 3.1 vs 6.5 ± 2.6 cm/year, $p < 0.00005$ ($n = 65$ and 30), respectively
  Year 2: 7.8 ± 2.1 vs 5.5 ± 1.9 cm/year, $p < 0.00005$ ($n = 55$ and 27), respectively
- Mean HtSDS (change over 2 years): GH group, –2.9 to –1.6 ($p < 0.00005$); placebo group, –2.8 to –2.9 (NS)
- Comparisons of change in height age minus change in BA did not indicate advancement of BA in treated group
- Roche–Wainer–Thissen PAH at 2 years: GH group, 5.4 cm increase; placebo group, 0.4 cm decrease ($p < 0.00005$)
- Weight gain: GH group, 6.7 ± 2.2 kg; placebo group, 4.6 ± 2.7 kg ($p = 0.0004$ after 2 years)
- TSF thickness: GH group, –1.6 ± 2.6 mm; placebo group, +0.6 ± 3.8 mm ($p = 0.006$)
- MAMC: GH group, 21 ± 1.1 cm; placebo group, 1.3 ± 1.2 cm ($p = 0.007$)
- Adverse events: No differences between groups in year 1. In year 2, asthma or wheezing occurred in 8 of 55 GH-treated patients and none of those receiving placebo. All episodes of asthma or wheezing were preceded by upper respiratory tract infections. "No clinically significant side-effects were associated with rhGH treatment"
- Drop-outs: GH group, 13 patients in year 1 and 13 patients in year 2; placebo group, 12 patients in year 1 and 3 patients in year 2

Additional biochemical measures are not reported

Comments

Methodological comments

- No information on randomisation, except that randomisation was performed to place 2 of 3 patients in treatment group and 1 of 3 patients in placebo group, and to maintain balance in age, sex, standardised height, degree of renal function and primary renal disease
- Blinding: No information
- Comparability of treatment groups: See randomisation comment
- Method of data analysis: Analysed by patients completing trial
- Attrition/drop-out: Percentages given. Relatively high, but comparable in groups (41% of drop-outs due to transplant, 24% due to patient or parent request)

General comments

- Generalisability: Inclusion/exclusion criteria well defined and should generalise to other renal insufficiency cases
- Outcome measures: Measures appropriate, although FH predictions questionable
- Intercentre variability: Not assessed
- Conflict of interests: Supported by Genentech

continued

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	GH group: 16% in year 1, 19% in year 2 Placebo group: 28% in year 1, 10% in year 2

Reference and design	Intervention	Patients	Outcome measures
Powell *et al.*, 1997[29] (USA) RCT Jadad score: 2/5	GH and untreated GH: 0.05 mg/kg/day s.c. (Nutropin) Dose adjusted at each visit (every 3 months) Control: untreated 1 year	69 patients entered, 44 analysed GH group: 30 patients 83% boys Age: 5.6 ± 2.0 years BA: 4.0 ± 1.5 years HtSDS: –2.7 ± 0.7 Weight for HtSDS: 0.0 ± 1.3 MAMC: 14.1 ± 1.6 cm TSF thickness: 7.9 ± 3.2 mm Control group: 14 patients 86% boys Age: 5.7 ± 2.6 years BA: 4.2 ± 1.8 years HtSDS: –2.7 ± 0.8 Weight for HtSDS: –0.2 ± 1.5 MAMC 14.4 ± 2.8 cm TSF 8.5 ± 3.2 mm Inclusion criteria: • Irreversible renal insufficiency (GFR > 10 and < 40 ml/minute/1.73 m^2 • Height < 5th percentile for age • Age > 2.5 years • Ability to stand for height measurement • BA < 10 years for girls and 11 years for boys • Tanner stage I	GV HtSDS BA MAMC TSF thickness Weight gain Anthropometric measures at 0, 3 and 12 months

Results (mean ± SD)

- GV (12 months): GH group, 9.1 ± 2.8 cm; no treatment group, 5.5 ± 1.9 cm ($p < 0.0001$)
- HtSDS (change over 12 months): GH group, 0.8 ± 0.5; no treatment group, 0.0 ± 0.3 ($p < 0.0001$)
- Weight gain (12 months): GH group, 3.5 ± 1.5 kg; no treatment group, 2.2 ± 1.0 kg ($p = 0.007$)
- MAMC (cm change from baseline): GH group, 1.2 ± 0.9; no treatment group, –0.2 ± 1.7 ($p = 0.0015$)
- TSF (mm change from baseline): GH group, –1.9 ± 2.5; no treatment group, 0.9 ± 1.2 ($p = 0.0003$)
- Increased growth in GH group was not associated with an acceleration in BA
- Adverse effects: No mention of adverse events, although 1 patient withdrew due to allergic reaction to GH injections

Additional biochemical results not reported here

20 patients exited in first year, 5 patients had insufficient serum for protein assays

Comments

Methodological comments

- Allocation to treatment groups: No information on method of randomisation, except that randomisation was conducted to enter 1 of 3 patients as controls and 2 of 3 patients in treatment group. Groups balanced for age, gender, height, GFR at baseline and nature of primary renal disease
- Blinding: No blinding – open label
- Comparability of treatment groups: No apparent differences between groups
- Method of data analysis: Analysis based on patients completing trial. Values converted to log 10 values for analyses. No CIs
- Sample size/power calculation: No power estimates for non-significant results
- Attrition/drop-out: Attrition described. Relatively high rate of withdrawal

General comments

- Generalisability: GFR requirement may limit generalisability to other patients with chronic renal insufficiency
- Outcome measures: Appropriate measures
- Intercentre variability: Not assessed; 26 centres included
- Conflict of interests: Grant from Genentech

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0 (open label)
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	36% of patients not available for analysis

Reference and design	Intervention	Patients	Outcome measures
Hokken-Koelega *et al.*, 1991[30] (International) Randomised crossover Jadad score: 4/5	GH and placebo GH, 4 IU/m^2, or equal volume of placebo s.c. once per day (Norditropin) 6 months in each condition	20 patients (16 completed trial) Age: 9.5 ± 3.4 years Group 1 (GH/placebo): 6 boys, 2 girls Age: 8.7 (4.4–11.3) years BA: 7.4 (3.7–10.2) years HtSDS: –2.3 (–3.9 to –1.8) GV: 1.6 (0–3.0) cm per 6 months Weight for height: 98.2% (86.7–113.5%) Group 2 (placebo/GH): 4 boys, 4 girls Age: 8.6 (4.4–16.0) years BA: 7.5 (3.7–10.6) years HtSDS: –2.7 (–5.6 to –2.0) GV: 1.4 (0.2–2.6) cm per 6 months Weight for height: 101.5% (90.3–116.5%) • CRF for ≥ 1 year • Creatinine clearance < 20 ml/minute/1.73 m^2 • HtSDS for age < –1.88 and height velocity for age < 25th percentile • Prepubertal (Tanner stage I) • BA < 10 years for girls and 12 years for boys • No evidence of growth retardation cause other than CRF • Normal thyroid function • No osteodystrophy • No previous treatment with anabolic steroids, sex steroids or recombinant human erythropoietin Setting: multicentre	GV GVSDS BA

Results (mean ± SD) (n =16)

- GV (cm per 6 months), first 6 months: GH group, 5.2 ± 1.2; placebo group, 2.4 ± 1.0 (both significantly greater than at baseline); GH group > placebo group ($p < 0.001$)
- GV (cm per 6 months), second 6 months (after crossover): GH group, 4.4 ± 1.6; placebo group, 1.5 ± 0.4
- Mean GH-induced increase in height velocity compared with placebo was 2.9 cm per 6 months (95% CI, 2.3 to 3.5 cm per 6 months), $p < 0.0001$
- GVSDS, first 6 months: GH group, 6.9 ± 2.4; placebo group, –0.5 ± 3.2
- GVSDS, second 6 months (after crossover): GH group, 5.0 ± 4.5; placebo group, –3.0 ± 1.6
- Increase in mean GVSDS during GH compared with placebo ($p < 0.0001$)
- Positive correlation between pretreatment GVSDS and increase in GVSDS during GH treatment, $r = 0.72$ (95% CI, 0.35 to 0.90)
- Negative correlation between CA and growth response during GH ($r = –0.59$; 95% CI, 0.13 to 0.84)
- Effect of GH on BA similar to that of placebo – bone maturation was not accelerated
- Adverse effects: No reported adverse effects

Additional biochemical results not reported here

4 patients withdrew due to kidney transplants

Comments

Methodological comments

- Allocation to treatment groups: Random
- Blinding: Double-blind
- Comparability of treatment groups: Groups appear comparable and, because all participated in both conditions, any existing differences are less relevant than in other designs
- Sample size/power calculation: No power estimates offered
- Attrition/drop-out: 20% of participants withdrew (kidney transplants)
- There was no wash-out period between treatment and placebo (and vice versa)

continued

***Comments* contd**

General comments

- Generalisability: Inclusion/exclusion criteria well defined and would appear to generalise to target population
- Outcome measures: Appropriate measures used
- Intercentre variability: Not assessed
- Conflict of interests: Supported by grant from Novo Nordisk A/S, Denmark

Baseline height expressed as SDS using Dutch reference data

GVSDS compared with references derived from the childhood phase of the Infant–Childhood–Puberty model

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	20%

Reference and design	Intervention	Patients	Outcome measures
Broyer, 1996[31] (International) RCT, open label Jadad score: 2/5	Year 1: GH and no treatment Year 2: all GH GH: 1 IU/kg/week s.c. daily administration (Genotropin) Control: untreated 2 years	GH group: 106 patients Age: 12.6 ± 3.4 years 53% prepubertal HtSDS: –3.2 ± 1.4 GV: 3.6 ± 2.2 cm/year Control: 97 patients Age: 12.1 ± 3.1 years 63% prepubertal HtSDS: –3.1 ± 1.1 GV: 4.0 ± 2.1 cm/year • HtSDS < –2 or GV < 25th percentile • Normal thyroid function • Post-renal transplantation (at least 12 months) • At least 2 separate height measurements over a minimum of 6 months • Minimum calculated GFR of 20 ml/minute/1.73 m^2 Setting: multicentre	ΔGV ΔHtSDS (changes relative to baseline) Incidence of rejection Auxological and routine biochemical assessments at 3-month intervals

Results (analyses separately for prepubertal, entering puberty and pubertal)

- **ΔHtSDS (mean ± SD):**
  Year 1 (treatment vs no treatment):
  Prepubertal: 0.6 ± 0.3 vs 0.1 ± 0.3
  Entering puberty: 0.6 ± 0.6 vs –0.1 ± 0.4
  Pubertal: 0.7 ± 0.5 vs 0.1 ± 0.5
  All treatment vs no treatment comparisons significant ($p < 0.0001$)

- **ΔGV (Δcm/year – mean ± SD):**
  Year 1 (treatment vs no treatment):
  Prepubertal (n = 28 vs 30): 3.7 ± 1.6 vs 0.3 ± 1.6
  Entering puberty (n = 9 vs 11): 4.9 ± 3.0 vs 0.6 ± 1.8
  Pubertal (n = 29 vs 18): 4.3 ± 2.2 vs 0.7 ± 2.1
  All treatment vs no treatment comparisons significant ($p < 0.0001$)

- **Adverse effects:**
  Statistical comparison of treatment vs no treatment GFR not reported

  Year 1: GH group, 22 rejection episodes in 16 patients (10 biopsy confirmed); control group, 9 rejection episodes in 7 patients (4 biopsy confirmed)

  Number of patients with acute rejection episodes higher in treatment than no treatment group among those with a history of more than one prior episode (11 and 3 patients, respectively)

Other biochemical results not reported here

Not included in analyses: 23 patients from renal function analyses; 72 patients from growth analyses (this n does not match n from results table, in which n for growth analyses = 125)

Comments

Methodological comments

- Randomised "centrally". No other information
- No blinding (open label)
- Baseline characteristics did not differ significantly, except that number of patients with high number of prior rejection episodes was higher in GH group
- Within-subject comparisons across time were confounded by changes in age, etc., and were therefore not reported. However, change outcomes were also based on changes from baseline within groups
- No power information.
- No information on withdrawals. High proportion of patients not included in analyses. Analyses based on patients remaining in trial

General comments

- Generalisability: Inclusion/exclusion criteria defined. Should not limit generalisability to other paediatric renal transplant patients. However, number of patients not included in analyses is a concern
- Outcome measures: Appropriate
- Intercentre variability: No assessment
- Conflict of interests: Study by Pharmacia & Upjohn

continued

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	35% from growth analyses

Reference and design	Intervention	Patients	Outcome measures
Hokken-Koelega *et al.*, 1996[32] (International) Randomised crossover Jadad score: 4/5	GH and placebo GH, 4 IU/m^2, or equal volume of placebo s.c. once per day (Norditropin) 6 months in each condition	11 patients Age: 12.1 ± 2.9 years (range, 8–18 years) Group 1 (GH/placebo): 5 boys, 1 girl Age: 12.1 (9.1–18.7) years HtSDS: –3.0 (–7.6 to –1.2) GV: 1.4 (0.5–2.6) cm per 6 months BMI SDS: 3.1 (–1.1 to 4.2) Group 2 (placebo/GH): 4 boys, 1 girl Age: 11.1 (8.3–14.9) years HtSDS: –2.6 (–3.6 to –2.1) GV: 0.8 (0.6 to 1.8) cm per 6 months BMI SDS: 1.3 (–0.2 to 3.7) Inclusion criteria: • Post-renal transplant (≥ 12 months) • Stable condition without rejection episodes (≥ 12 months) • HtSDS for age < –1.88 with height velocity for age < 50th percentile, or height SDS > –1.88 with height velocity < 25th percentile • Prepubertal (Tanner stage I) • BA < 10 years for girls and 12 years for boys • Prednisone dose ≤ 0.25 mg/kg/day for ≥ 6 months • No evidence of growth retardation cause other than following renal transplant • Normal thyroid function and acid–base balance • No previous treatment with sex steroids Setting: multicentre	GV GVSDS BA

Results (mean ± SD)

- GV (cm per 6 months), first 6 months: GH group, 5.3 ± 1.0; placebo group, 1.9 ± 0.7 (significant increase over baseline in GH group [$p < 0.0001$] and marginal in placebo group [$p = 0.06$])
- GV (cm per 6 months), second 6 months: GH group, 3.9 ± 1.3; placebo group, 1.5 ± 0.9
- Mean GH-induced increase in GV compared with placebo was 2.9 cm per 6 months (95% CI, 1.9 to 3.9; $p < 0.0001$)
- GVSDS, first 6 months: GH group, 9.1 ± 2.9; placebo group, –0.4 ± 1.7
- GVSDS, second 6 months: GH group, 5.3 ± 4.0; placebo group, –1.3 ± 2.9
- Increase in mean GVSDS during GH compared with placebo ($p < 0.0001$)
- Effect of GH on BA similar to that of placebo – bone maturation was not accelerated
- Increase in GVSDS due to GH tended to be greater for children whose pretreatment GVSDS was relatively high ($r = 0.43$, $p = 0.19$)
- Significant decrease of BMI SDS during GH treatment compared with placebo (–0.6 SD, $p < 0.001$)
- Adverse effects: "no serious adverse effects". No patients had an acute rejection episode during the study

Additional biochemical results not reported here

No withdrawals

Comments

Methodological comments

- Allocation to treatment groups: Random
- Blinding: Double-blind
- Comparability of treatment groups: Groups appear similar, although those starting on GH were slightly older, had higher BA, were growing more and had a considerably greater BMI. However, because all patients participated in both conditions, any existing differences are less relevant than in other designs
- Sample size/power calculation: No power estimates offered
- Attrition/drop-out: None
- No washout period between treatment and placebo (and vice versa)

General comments

- Generalisability: Inclusion/exclusion criteria well defined and would appear to generalise to target population
- Outcome measures: Appropriate measures used
- Intercentre variability: Not assessed
- Conflict of interests: Supported by grant from Novo Nordisk A/S, Denmark

Baseline height relative to Dutch reference data

Height velocity SDS compared with height velocity references derived from the childhood phase of the Infant–Childhood–Puberty model and adapted for wide age ranges

continued

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	1 + 1
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	0

GFR, glomerular filtration rate; TSF, triceps skinfold; MAMC, mid-arm muscle circumference

Appendix 16

Summary of evidence of effectiveness of GH in CRF: non-RCTs reporting final height

Reference and design	Intervention	Patients	Outcome measures
Haffner *et al.*, 2000[50] (Germany) Non-randomised treatment/no treatment Unclear whether prospective or retrospective Mix of CRF and post-transplant patients	GH: 1 IU (0.33 mg)/kg/week in daily s.c. injections in evening (Genotropin) Median duration of GH: 5.3 years 14 patients discontinued treatment before attaining FH but were followed to FH Other interventions used	142 patients treated for ≥ 1 year and remained prepubertal for at least the first year of treatment 38 children reported at FH Age: 10.4 ± 2.2 years BA: 7.1 ± 2.3 years HtSDS: –3.1 ± 1.2 50 children with CRF were controls. Matched to treated children in age at first observation, underlying renal disease, treatment during observation period, mean residual renal function or renal allograft function, and cumulative dose of glucocorticoids. Untreated because exhibited little or no growth retardation at baseline, declined participation or were ineligible because of advanced puberty Inclusion criteria: • Participants in multicentre study of children with CRF in Germany • Height SDS ≤ –2 or height velocity below 25th percentile during the year before treatment • GFR < 60 ml/minute/1.73 m^2 for children not on dialysis or > 20 ml/minute/1.73 m^2 for those who had received a renal allograft	Height SDS FH (cm)

Results (mean ± SD) (n = 38)

- FH (cm):
  Boys: GH group, 165.2 ± 8.2; control group, 162.1 ± 9.1 ($p = 0.021$)
  Girls: GH group, 156.2 ± 9.8; control group, 151.9 ± 6.7 ($p = 0.028$)
- Mean final HtSDS: GH group, –1.6 ± 1.2 (increase 1.4 SDS; $p < 0.001$ for comparisons with pretreatment); control group, –2.1 ± 1.2 (decrease 0.6 SDS; $p < 0.001$ for comparison with pretreatment)
- Comparison with target heights: GH group, –10.1 cm in boys ($p = 0.005$) and –12.1 cm in girls ($p = 0.007$); control group, –15.8 cm in boys and –16.1 cm in girls ($p < 0.001$ for both comparisons)
- Comparison with predicted height: GH group, 1.8 cm over prediction in boys ($p = 0.10$) and no significant change in prediction in girls; control group, –10.3 cm change from prediction ($p < 0.001$ for comparisons for boys and girls separately)
- Multiple regression: Absolute height gain and HtSDS gain related to longer duration of the prepubertal and pubertal observation periods, longer duration of GH therapy, greater initial target-height deficit, lower percentage of time spent on dialysis and male sex
- Adverse effects: No mention

Comments

Methodological comments

- Allocation to treatment groups: Non-randomised, self-selected
- Blinding: Open study
- Comparability of treatment groups: Control patients (boys) were significantly taller than treated patients at baseline when considering absolute height (cm). Both control boys and girls were taller than treated patients when considered in HtSDS. PAHs of control patients were also significantly greater than those of treated patients at baseline
- Method of data analysis: Hypothesis tests but no CIs
- Sample size/power calculation: None
- Attrition/drop-out: None mentioned

continued

Comments

General comments

- Generalisability: Criteria described and seem representative
- Outcome measures: Measures seem appropriate, although applying prediction methods in abnormal populations may be questionable
- Intercentre variability: Not assessed
- Conflict of interests: Supported by Pharmacia & Upjohn, Stockholm, Sweden

Final adult height definition: Height velocity < 1 cm/year or by evidence of epiphyseal closure on radiography of the hand

Reference data taken from the Zurich Longitudinal Growth Study

Genetic target height: Mid-parental height + 10 cm for boys and – 2.6 cm for girls

PAH calculated by Tanner method

"To minimise the influence of measurement errors, the height data were smoothed by kernel estimation, a mathematical procedure that applies moving weighted averages to raw data." (pages 924–5 of the paper)

"A synchronisation program was applied that transforms the time scale of each individual curve to align the characteristic points with their respective means." (page 925 of the paper)

Short-term growth results were considered in the report, but because there are higher-quality trials reporting short-term growth, these results are not summarised here

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Self-selected into trial or not
Proper sampling sample			✗			Neither random nor consecutive
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria	✗					
Reported attrition				✗		No mention of attrition
Comparability of groups			✗			Control group taller at baseline
Generalisability	✗					

Reference and design	Intervention	Patients	Outcome measures
Janssen *et al.*, 1997[51] (Belgium) Retrospective comparison of GH-treated patients with historical control	GH: 1 IU/kg/week daily s.c. injections in evening (Genotropin) Median duration: 3.4 years All on immuno-suppressive therapy (either 2 or 3 agents)	36 short children with renal allograft treated with GH 17 who reached FH and were treated > 1 year are reported here (some patients were included in Broyer report[31]) 10 boys, 7 girls: Median age: 14.0 (11.3–16.9) years Median BA: 10.6 (7.6–14.0) years Median HtSDS (at GH start): –2.5 (–5.6 to 2.1) Median height (at GH start): 133.4 (126.5–148.3) cm Median target height: 160.5 (159.1–165.3) cm Historical control group of 14 patients (7 boys, 7 girls) who received allografts with same immunosuppressive therapy and transplant strategy. Matched for age at transplantation, dose of prednisolone and HtSDS at time of transplantation • Height below 3rd percentile or height velocity below 25th percentile • ≥ 12 months after transplantation • Normal thyroid function • Normal levels of HbA_{1C} and albumin Setting: two paediatric centres	HtSDS Height (cm) ΔHeight

Results (medians)

- Final HtSDS: GH group, –1.8 in boys, –1.9 in girls; historical control group, –3.2 in boys, –3.2 in girls
- Median FH: GH group, 162.7 cm in boys, 151.0 cm in girls; historical control group, 153.5 cm in boys, 143.0 cm in girls
- FH comparison with controls: Height and HtSDS greater in treated than untreated boys ($p = 0.01$); no significant differences in girls
- ΔHtSDS: GH group, 1.3 in boys (median duration, 2.9 years), 0.5 in girls (median duration, 3.4 years)
- BA: Not accelerated during GH therapy
- Adverse effects: Bone deformities in two patients; clinical facial dysmorphias in three patients, with a worsening of prognathism and increased fleshiness of the nose and chin. One patient suffered from lipolysis. There was no mention as to whether these effects were attributed to GH treatment. Graft survival and acute rejection were considered in all 36 treated patients. During treatment, there were five chronic rejections, with two transplant glomerulopathies and four acute rejections in the presence of a chronic rejection. GH was stopped in these patients, but three returned to dialysis 1, 2 and 5 years later

Comments

Methodological comments

- Allocation to treatment groups: Retrospective, non-randomised
- Blinding: Open treatment
- Comparability of treatment groups: Matched controls, but there may be differences due to history
- Method of data analysis: Hypothesis tests but no CIs
- Sample size/power calculation: None
- Attrition/drop-out: 19.4% of original group dropped out

General comments

- Generalisability: Criteria defined; patients seem representative of target group
- Outcome measures: Outcomes seem appropriate
- Intercentre variability: Not assessed
- Conflict of interests: Pharmacia & Upjohn thanked for logistical support

Height expressed as SDS according to Tanner

Target height was mid-parental height

Considered FH normal when target height ± 8 cm was reached

Patients were assumed to have reached FH when pubertal maturation was complete (A3 P4-5 M5 or G5) and when height velocity was < 0.5 cm/year

Although height velocity was cited in the report, it is not mentioned here because there are studies of higher quality that report short-term outcomes

continued

Quality assessment (revised from Spitzer* et al., *1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Retrospective/historical control
Proper sampling			✗			Neither random nor consecutive sample
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria	✗					
Reported attrition	✗					19.4% of original sample lost
Comparability of groups	✗					
Generalisability	✗					

Appendix 17

Summary of evidence of effectiveness of GH in PWS: RCTs

Reference and design	Intervention	Patients	Outcome measures
Carrel *et al.*, 1999[33] (USA) Study type/design: open RCT (Same study as Myers *et al.*, 1999,[105] each reporting slightly different outcome measures) Jadad score: 2/5	GH: 1 mg/m^2/day (Nutropin) Control : no treatment Length of treatment: 1 year Other interventions used: not stated	*n* = 54 GH group: 35 patients 42% girls Age: 9.8 years HtSDS: –1.1 ± 1.3 GV: 4.72 ± 2.2 cm/year GVSDS: –1.0 ± 2.5 BA: 9.1 ± 3.6 years Control group: 19 patients 58% girls Age: 10.0 years HtSDS: –1.5 ± 0.8 GV: 5.18 ± 1.5 cm/year GVSDS: –0.9 ± 1.7 BA: 8.4 ± 3.1 years Characteristics of target population: • PWS genetically confirmed • No prior GH therapy Setting: not specified	HtSDS GV GVSDS Body fat % Lean mass (kg) BMI (kg/m^2) Length of follow-up: 6 months observation plus 1 year of treatment

Results (mean ± SD) (some results abstracted from each paper)

- HtSDS: GH group, –0.6 ± 1.2; control group, –1.6 ± 1.2 ($p < 0.01$)
- GV: GH group, 10.1 ± 2.5 cm; control group, 5.0 ± 1.8 cm ($p < 0.01$)
- GVSDS: GH group, 4.6 ± 2.9; control group, –0.7 ± 1.9 ($p < 0.01$)
- Body fat %: GH group, 38.4% ± 10.7%; control group, 45.8% ± 8.8% ($p < 0.01$)
- Lean mass (kg): GH group, 25.6 ± 4.3; control group, 21.7 ± 5.0 ($p < 0.01$)
- BMI (kg/m^2): GH group, 23.7 ± 6.3; control group, 25.2 ± 8.9 (NS)
- Adverse effects: Headaches in two patients treated with GH within first 3 weeks. Symptoms resolved with temporary cessation and gradual re-institution of GH

Comments

Methodological comments

- Allocation to treatment groups: Reported as randomised. Method not stated
- Blinding: None
- Comparability of treatment groups: Baseline comparability
- Method of data analysis: Not specifically stated as ITT
- Sample size/power calculation: No report of *a priori* power calculation
- Attrition/drop-out: Not stated; however, results tables suggest no drop-outs

General comments

- Generalisability: Broad inclusion criteria were defined. Consecutive patients sampled. Wide age range. Included pubertal and prepubertal children
- Outcome measures: Short-term study; FHs not reached. Primary outcomes were metabolic rather than height measures. Assessment was not blinded
- Conflict of interests: Supported by Genentech foundation for growth and development

Additional body composition and biochemical outcomes not reported here

Reference group for SDS measures was not reported

continued

Quality assessment for RCTs (Jadad score)

Question	**Score**
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1 None were reported
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	0%

Reference and design	Intervention	Patients	Outcome measures
Lindgren *et al.*, 1997[34] and 1998[35] (Sweden and Denmark) Study type/design: RCT 2 years: year 1, GH vs control (no treatment); year 2, two doses of GH Only year 1 data reported Jadad score: 2/5	GH: 0.1 IU/kg/day (Genotropin) Control: no treatment	29 patients enrolled, 27 patients analysed GH group: 15 patients Age: 6.8 (3.6–11.9) years BA: 6.6 (3.3–13.0) years Sex: 7 girls, 8 boys Target HtSDS: 0.4 ± –1.3 to 1.8) HtSDS: –1.6 (–4.0 to 0.5) GVSDS –1.9 (–6.4 to 0.9) BMI SDS: 3.0 (–0.7 to 7.6) Fat-free mass: 14.9 ± 4.1 kg Body fat: 40.0% ± 10.5% Control group: 14 enrolled, 12 analysed Age: 6.4 (3.3–11.7) years BA: 5.4 (3.3–10.2) years Sex: 5 girls, 7 boys Target HtSDS: –0.1 (–1.5 to 1.0) HtSDS: –1.7 (–5.3 to 0.4) GVSDS: –0.1 (–1.7 to 2.71) BMI SDS: 2.1 (–1.3 to 5.1) Fast-free mass: 14.1 ± 3.0 kg Body fat: 34.8% ± 7.9% Characteristics of target population: • Prepubertal • Aged 3–12 years • PWS (Holm 1993 criteria) Setting: not specified	HtSDS GVSDS BMI SDS Fat-free mass (DEXA) Body fat % (DEXA) Length of follow-up: observation for 6 months, treatment for 2 years, observation for 6 months, for total of 3 years Only year 1 reported here

Results (mean and range)

- HtSDS: GH group, –0.4 (–2.7 to 1.9) ($p < 0.05$ compared to baseline); control group, –1.8 (–5.1 to 0.2)
- GVSDS: GH group, +6.0 (1.4 to 11.9) ($p < 0.05$ compared to baseline); control group, –1.4 (–3.2 to 0.3)
- BMI SDS: GH group, 2.0 (–2.4 to 6.7) ($p < 0.05$ compared to baseline); control group, 2.5 (0.1 to 6.1)
- Fat-free mass (mean ± SD): GH group, 19.8 ± 5.2 kg ($p < 0.001$ compared to baseline); control group, 15.2 ± 2.9 kg
- Body fat (mean ± SD): GH group, 30.9% ± 11.4% ($p < 0.001$ compared to baseline); control group, 38.2% ± 9.1%
- Adverse effects: One boy developed low thyroxine levels on GH treatment, without change in TSH levels. He received substitution with L-thyroxine during GH treatment. Increased levels of fasting insulin during treatment may be regarded as 'laboratory adverse events'. Insulin levels were still within the normal range. Increased insulin levels declined after cessation of treatment

Comments

Methodological comments

- Allocation to treatment groups: Lindgren 1997 study was randomised (method not reported)
- Blinding: None reported
- Comparability of treatment groups: Baseline comparability
- Method of data analysis: Comparisons from baseline were reported, rather than comparison between treatment groups. Some results were presented graphically with no reporting of values. Appears to be considerable individual variability in response, which was not commented on in the report
- Sample size/power calculation: No *a priori* calculations. Small sample size
- Attrition/drop-out: Lindgren 1997 study reported 2 children in control group excluded (due to scoliosis and precocious puberty)

General comments

- Generalisability: Inclusion criteria were defined. Methods used to select sample were not reported
- Outcome measures: Appropriate and objective. Methods used to measure height were not reported
- Conflict of interests: Not stated

Fat-free mass and % body fat measured by DEXA

BA: Based on Tanner–Whitehouse standard

Height and weight SDS: Reference material from healthy Swedish children (Karlberg, 1976)

Projected height: Based on syndrome-specific growth charts (Butler, 1991)

Additional biochemical and body composition outcomes not reported here

continued

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall drop-outs: 2/29 (7%) GH: 0/15 (0%) Control: 2/14 (14%)

Reference and design	Intervention	Patients	Outcome measures
Hauffa, 1997[5] (Germany) Study type/design: open RCT, single centre Jadad score: 2/5	GH: 0.075 IU/kg/day for first month, then continued at dose of 0.15 IU/kg/day, up to a maximum of 8 IU/day Control: untreated Length of treatment: 1 year Other interventions used: not stated	19 patients randomised, 17 entered (16 analysed) GH: 8 patients (data from 7) CA: 8.25 ± 2.4 years BA: 7.91 ± 4.3 years Sex: 5 boys, 4 girls Height: 120.9 ± 16.3 cm Target height: 172.9 ± 8.5 cm Control: 9 patients CA: 7.56 ± 2.0 years BA: 6.76 ± 2.4 years Sex: 5 boys, 4 girls Height: 120.5 ± 11.2 cm Target height: 174.8 ± 8.2 cm Characteristics of target population: • Prepubertal • Aged 3–12 years • PWS (confirmed by molecular genetics) • Projected FH < 3rd percentile for German population Setting: university children's hospital	ΔHtSDS GVSDS Length of follow-up: 1 year

Results (mean ± SD)

- ΔHtSDS: GH group, +1.07; control group, –0.25
- GVSDS: GH group, +5.5; control group, –2.3 (p = 0.0012)
- Adverse effects: One boy in GH group developed pseudotumour cerebri 2 weeks after increasing the starting dose of GH to the final dose. Symptoms resolved after GH stopped. After several weeks, GH treatment resumed at half the previous dose. This dose was well tolerated
- Significant increases in IGF-I and IGFBP-3 in GH-treated children

Comments

Methodological comments

- Allocation to treatment groups: Randomised (method not stated)
- Blinding: Not stated
- Comparability of treatment groups: Baseline comparability
- Method of data analysis: Appropriate, although no indication was given of range of results among individuals
- Sample size/power calculation: Not reported.
- Attrition/drop-out: 19 patients randomised, 2 not entered (reasons not stated), 1 not included in analysis

General comments

- Generalisability: Methods used to select patients were not described. Inclusion criteria were defined
- Outcome measures: Short-term study, and FH not reached. Methods used to measure children were not described
- Conflict of interests: Technical and financial support from Pharmacia & Upjohn, Germany

Growth standard: American children with PWS

Discussion of additional biochemical outcomes not presented here

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 (method not described)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 2 out of 19 patients not entered. Not described by treatment group. One patient in GH group not analysed

Reference and design	Intervention	Patients	Outcome measures
Whitman *et al.*, 2000[36] (USA) RCT Jadad score: 2/5	GH: 1mg/m^2/day (Nutropin) No treatment 6-month growth assessment period, 12 months of treatment	GH group: 35 patients No treatment group: 19 patients Patient characteristics: • Consecutive PWS genetically confirmed • Aged 4–16 years • BA < 13 years for girls and < 15 years for boys Exclusion criteria: • Prior therapy with GH • Scoliosis > 20°	Offord Survey Diagnostic Instrument (behavioural checklist) Marital Satisfaction Inventory Family Inventory of Life Events

Results (mean ± SD)

- Attention: GH group, 9.25 ± 3.7; no treatment group, 8.77 ± 4.5 (NS)
- Depression: GH group, 7.84 ± 4.8; no treatment group, 7.2 ± 1.9 (NS); within-group before/after comparison in no treatment group (reduction of symptoms, $p < 0.05$)
- Compulsion: GH group, 3.35 ± 1.8; no treatment group, 3.44 ± 2.9 (NS); within-group before/after comparison in treated group (reduction of symptoms, $p < 0.05$)
- Anxiety: GH group, 5.05 ± 5.1; no treatment group, 3.89 ± 3.6 (NS)
- Violence: GH group, 2.9 ± 3.1; no treatment group, 1.89 ± 2.7 (NS)
- Psychoses: GH group, 2.05 ± 2.0; no treatment group, 1.78 ± 1.9 (NS)
- "A significant positive effect (reduction of symptoms) was noted for the treatment group from baseline to time one on both depression and obsessive symptoms"
- No differences between groups on range of symptoms associated with PWS (e.g. arguing, obsessional thoughts, destroying property and stealing food)
- Significant within-group changes in obsessional thoughts and skin-picking in GH group from baseline to 12 months on treatment: obsessional thoughts, 1.56 at baseline, 1.29 on treatment ($p < 0.05$); skin-picking, 1.38 at baseline, 1.08 on treatment ($p < 0.05$)
- Adverse effects: No apparent behavioural deterioration; no other mention

Results were from behavioural questionnaires completed by mothers for 27 GH-treated and 14 untreated patients. Data restricted to those who completed questionnaires at all assessment points

Comments

Methodological comments

- Allocation to treatment groups: Not described
- Blinding: No mention
- Comparability of treatment groups: Groups appear comparable, although treatment group may have had slightly higher symptomatology
- Method of data analysis: Hypothesis tests. No adjustments for multiple comparisons
- Sample size/power calculation: No mention
- Attrition/drop-out: 23% of treated and 26% of untreated patients did not complete questionnaires and were not included in analyses

General comments

- Generalisability: Patients appear representative
- Outcome measures: Outcome measures seem reasonable, although not all were reported
- Intercentre variability: Not assessed
- Conflict of interests: Grant from Pharmacia Corporation

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	23% of treated and 26% of untreated patients not included in analyses

DEXA, dual-energy X-ray absorptiometry

Appendix 18

Summary of evidence of effectiveness of GH in PWS: non-RCT reporting final height

Reference and design	Intervention	Patients	Outcome measures
Angulo *et al.*, 2000[52] (USA) Single cohort	GH: 0.2–0.25 mg/kg/week (divided 3–7 days/week) Length of treatment: 4–10 years	16 children Patient characteristics: • PWS • 11 boys, 5 girls • Documented GHD • Age at start: 8.4 ± 2.5 years • Age at completion: 16 ± 1.5 years • Height SDS at start: –1.84 ± 1.56 cm • Parental target height: 170.5 ± 7.6 cm	FH (cm) Final HtSDS

Results (mean ± SD)
- FH: boys, 170 ± 10 cm; girls, 159 ± 4 cm
- Final HtSDS: –0.2 ± 1.3 ($p < 0.0001$)
- Adverse effects: No mention

FH definition: GV < 2 cm/year or BA > 16 years in boys and 14 years in girls

Comments

Methodological comments
- Single-group study with no information about sampling
- Attrition/drop-out: No information on attrition, appears retrospective

General comments
- Report available in abstract only
- Generalisability: Little information about patient sample. Patients were within normal height range at start and therefore may not be typical
- Outcome measures: Measures appropriate, but no comparison with untreated group
- Intercentre variability: Appears to be single centre
- Conflict of interests: No mention

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment					✗	Single group
Proper sampling				✗		No information
Adequate sample size				✗		No power calculations
Objective outcomes	✗					
Blind assessment					✗	Single group
Objective eligibility criteria					✗	Retrospective
Reported attrition					✗	Retrospective
Comparability of groups					✗	Single group
Generalisability				✗		Insufficient information to assess

Appendix 19

Summary of evidence of effectiveness of GH in ISS: RCTs

Reference and design	Intervention	Patients	Outcome measures
McCaughey *et al.*, 1998[37] (UK) Study type/design: RCT with second control group who did not consent to randomisation Jadad score: 2/5	Treatment arms: GH, 30 IU/m^2/week daily s.c. injections (Genotropin) Randomised untreated controls Non-randomised untreated controls Mean length of treatment: 6.2 years Other interventions used: none reported	Total number: 40 girls GH group: 10 girls Randomised controls: 8 girls Non-consent controls: 22 girls Characteristics of target population: • Normal girls of height ≥ 2 SD below mean height for age Participants: • Mean age at start of treatment, 8.07 ± 0.48 years • All had reached at least Tanner stage IV breast development and menarche before stopped treatment Setting: selected from community screening at school entry (Wessex Growth Study)	Height HtSDS Pubertal data: Height Mean age of peak velocity Mean amplitude of peak height velocity Mean age at menarche NFH data: Height HtSDS GV NFH minus target height NFH minus predicted height BA advancement Biochemical profiles Length of follow-up: length of treatment (mean, 6.2 years; range, 5.5–6.5 years)

Results (mean ± SD; ITT analysis, not specified)

NFH data (statistical significance reported for GH group vs control group combined with non-consent group, because their growth pattern is the same, and no differences were noted between initial and final HtSDS):

- Height: GH-treated group, 155.3 ± 6.4 cm; control group, 147.8 ± 2.6 cm; non-consent group, 149.3 ± 3.3 cm (p = 0.003; GH group 7.5 cm and 6 cm taller than control and non-consent groups, respectively)
- HtSDS: GH-treated group, –1.14 ± 1.06; control group, –2.37 ± 0.46; non-consent group, –2.13 ± 0.55 (p = 0.004)
- HtSDS change: From first to last assessment, change was significant only in GH-treated group (change, –1.35; p = 0.008)
- GV: GH group, 0.6 cm/year; controls, 1.0 cm/year; non-consent group, 1.6 cm/year at NFH (p = 0.211)
- Mean age of NFH: GH-treated group, 16.35 years; control group, 16.08 years; non-consent group, 15.93 years (p = 0.149)
- Current height minus target height: GH-treated group, 1.9 ± 5.1 cm; control group, –10.6 ± 4.3 cm; non-consent group, –5.1 ± 5.5 cm (p = 0.001)
- Current height minus predicted height: GH-treated group, 3.5 ± 4.4 cm; control group, –6.0 ± 1.7 cm; non-consent group, –5.3 ± 3.0 cm (p < 0.001)

Pubertal data:

- Mean age at menarche: 13.6 years (no significant difference between groups)
- Mean age of peak velocity: GH group, 11.7 years; control group, 12.2 years; non-consent group, 12.4 years (p = 0.266)
- Mean amplitude of peak height velocity: GH group, 7.6 cm/year; control group, 8.3 cm/year; non-consent group, 8.0 cm/year (p = 0.344)
- BA advancement: GH group gained 6.5 years, control group, 7.9 years. Significant difference at baseline (GH group had delay of 0.25 years, control group 0.89 years)

Adverse effects:

- Mean fasting insulin concentrations (8 treated patients and 6 controls): before puberty, only significant difference between groups was in year 4. No significant difference after puberty
- IGF-I: Before puberty, significant difference between groups in years 2, 3, 4 and 5. No significant difference after puberty

continued

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported
- Blinding: None
- Comparability of treatment groups: No significant difference between groups regarding mean pattern of growth, height, HtSDS or proportion with familial short stature. Significant different at baseline regarding difference between BA and CA, and mean target height. Higher GV in non-consenting controls compared to other groups
- Method of data analysis: Per protocol and not ITT analysis. Point estimates and CIs of differences between groups were not given. Data analysed with SPSS. Means of paired data compared with Student's *t*-test, unpaired data with Student's *t*-test or one-way ANOVA. Mann–Whitney *U* or Kruskal–Wallis tests used as appropriate for small numbers
- Sample size/power calculations: Very small sample size with no prior power calculation
- Attrition/drop-out: Drop-outs described with reasons and by treatment allocation group. GH group, 30%; untreated control group, 25%; non-consent control group, 14%

General comments

- Generalisability: Inclusion/exclusion criteria were defined. Exclusion criteria: children with disorders (references given but no details in report), coeliac disease. References given for tests used to exclude pathology but no details in text
- Outcome measures: Appropriate outcome measures used. Tanner–Whitehouse data used for children's standards
- Intercentre variability: Appears to be only one centre involved
- Conflict of interests: Support from Pharmacia & Upjohn Ltd

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 (no method)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall drop-out rate from RCT: 28% (5/18) GH-treated group: 30% (2/10) Untreated control group: 25% (2/8) Non-consent control group: 14% (2/22)

Reference and design	Intervention	Patients	Outcome measures
Genentech Collaborative Study Group, 1989[38] (USA) Multicentre RCT Jadad score: 1/5	Treatment arms: GH, 0.1 mg/kg by s.c. injection, three times a week (Genentech) No treatment Length of treatment: 1 year Other interventions used: not stated	Total: 121 children (74% boys) GH group: 63 children (73% boys) Controls: 58 children (74% boys) Characteristics of target population: • ISS • Age: ≥ 5 years • Height: ≥ 2 SD below mean (< 3rd percentile) • Birth weight: ≥ 2.5 kg • Serum GH: ≥ 10 ng/ml on at least one test • BA: girls, ≤ 9 years; boys, ≤ 10 years • Prepubertal Participants: • Mean age: control group, 9.5 years; GH-treated group, 9.4 years • Mean HtSDS: –2.8 ± 0.5 • BA: control group, 7.7 years; GH-treated group, 7.9 years • Height velocity: 4.4 ± 2.1 cm/year • Mean parental height less than mean for normal population • PAH: significantly less than normal adult height Setting: not specified	Outcomes: GV BA IGF-I SDS for PAH GH/IGF-I status assessed after stimulation with clonidine Fasting blood glucose Serum thyroxine Length of follow-up: 1 year

Results (mean ± SD, not ITT analysis)

Baseline to 1 year for prepubertal children (GH group, 50 patients; control group, 44 patients):

- GV (cm/year): GH group, from 4.7 ± 1.2 to 7.3 ± 1.2; control group, from 4.4 ± 1.3 to 4.7 ± 1.1 (GH significantly greater than baseline and control values at one year, $p < 0.00005$). Abstract reports different results: GH group, from 4.6 ± 1.1 to 7.5 ± 1.2; control group, from 4.2 ± 1.3 to 5.0 ± 1.40
- BA (years): GH group, from 7.6 ± 1.7 to 8.6 ± 1.7; control group, from 7.2 ± 2.1 to 8.2 ± 2.0 (no significant difference)
- PAH SDS: GH group, from –2.7 ± 0.5 to –2.2 ± 0.6 ($p = < 0.00005$, statistically significant increase in PAH SDS in GH-treated group but not in control group; determined using Bayley and Pinneau, Roche, and Tanner methods). Significance of difference between treatment groups was not reported

Baseline to 1 year for pubertal children (GH group, 13 patients; control group, 10 patients):

- Height velocity (cm/year): GH group, from 4.3 ± 0.8 to 8.4 ± 0.9 ($p = 0.001$); control group, from 3.5 ± 0.6 to 6.0 ± 2.2

Adverse effects: No adverse effects of therapy for treated group

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported. Stated to be randomised to ensure balance with respect to potential prognostic variables (pre-treatment IGF-I, height, age, BMI and maternal height)
- Blinding: Assessor of BA was blinded. Otherwise no blinding was reported
- Comparability of treatment groups: Comparable at baseline (data presented)
- Method of data analysis: Mean and SD. Student's *t*-test for comparison with baseline and between groups. Pearson correlation for pairs of variable. Point estimates and CIs of differences between treatment groups were not reported. Not analysed on ITT basis. Only prepubertal patients were included in the main analysis. No reasons given for exclusion of four patients in the control group from the analysis. PAH determined using Bayley and Pinneau, Roche, and Tanner methods
- Sample size/power calculations: No power calculation
- Attrition/drop-out: Not reported

General comments

- Generalisability: Inclusion and exclusion criteria were defined. Exclusion criteria: diabetes mellitus, hypothyroidism, chronic systemic illness, malignancy, bone/cartilage dysplasia, psychosocial dwarfism, previous history GH treatment, treatment for hyperactivity. Subsequently, children who had progressed into puberty (plus four others) were excluded from the analysis
- Outcome measures: FH not assessed. Short-term study for GH vs control (1 year)
- Intercentre variability: Not assessed. Study conducted at ten sites
- Conflict of interests: Study conducted by Genentech, California

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	None reported as drop-outs, but 4 patients excluded from prepubertal analysis

Reference and design	Intervention	Patients	Outcome measures
McCaughey *et al.*, 1994[39] (UK) Study type/design: RCT Jadad score: 2/5	Treatment arms: GH, 30 IU/m^2/week by daily s.c. injections (autoinjector, (Genotropin) Untreated control Length of treatment: 3 years Other interventions used: none reported	Total: 41 children GH-treated group: 21 children (52% boys) Controls: 20 children (60% boys) Characteristics of target population: • Prepubertal • Short normal children of similar age and social class • Height > 2 SD below mean (Tanner–Whitehouse) • Adequate stimulated GH Participants: • Mean age: 7.8 ± 0.5 years at entry • GH concentration: > 7.5 µg/l (15 mU/l) response to either clonidine or sleep • Mean birth weight: GH-treated group, 2800 g; control group, 2813 g Setting: selected from community (no details)	HtSDS GV GVSDS FH/NFH (not defined) Predicted FH Bone maturation Body composition Echocardiography Metabolic data Compliance Length of follow-up: 3 years

Results (not reported as ITT analysis)

Data from baseline to 3 years:

- Mean HtSDS: GH group, from –2.4 to –1.2 SD (12th percentile), vs control group, no change from –2.4 to –2.4 ($p < 0.001$)
- HtSDS corrected for BA: GH group, from –2.2 to –1.2, vs control group, no change from –1.7 to –1.7 ($p < 0.0001$)
- GV at 3 years: GH group, 6.4 cm/ year (95% CI, 5.26 to 7.54 cm/year), vs untreated group, 5.2 cm/ year (95% CI, 4.22 to 6.18 cm/year) ($p < 0.003$), with 95% CI calculated by L McIntyre from Table 1 of the report
- GV SDS: Greater in GH-treated group than in untreated group (0.74 vs –0.25, respectively)
- FH: Heights after 3 years of GH treatment "lying between third and 33rd centiles"
- Predicted FH: Mean improvement in GH group, 7.2 cm overall (10.3 cm for boys, 4.0 cm for girls); untreated control group, 1.4 cm overall (3.4 cm for boys, –0.6 cm for girls)
- Bone maturation: Mean BA increment in GH group, 3.1 years; untreated control group, 3.3 years. CA increase of 3.1 years in both groups
- Body composition: After 3 years, GH-treated children were significantly leaner than untreated group (body fat, 13.5% vs 17.9%, respectively; $p < 0.015$). Maximum fat loss was in first 6 months

Adverse effects:

- Drop-outs in GH group: Dislike of injections, 1/21; developed acne that persisted after withdrew, 1/21; lack of parental support, 4/21
- Drop-outs in control group: 6 patients withdrawn from intensive monitoring due to dislike of annual blood tests in control group, 1/20; developed asthma requiring steroids, 1/20; lack of parental support, 2/20; moved, 2/20
- However, height data regularly collected for all

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported
- Blinding: Assessor of BA was blinded. No mention made of blinding of other outcomes assessed
- Comparability of treatment groups: Reported as similar at baseline on age, sex, height, parental height, birth details, BA delay, socio-economic status and evidence of psychosocial deprivation (no supporting data)
- Method of data analysis: Analysis not reported as being on ITT basis. Point estimates and CIs of difference between groups were not reported. Used *t*-tests and Mann–Whitney tests to compare groups
- Sample size/power calculations: No power calculations. Small sample size lacking power to detect significant differences in some outcomes (e.g. metabolic changes) between groups
- Attrition/drop-out: Drop-outs described with reasons and by treatment allocation group. GH-treated group drop-out rate was 29% (6/21) vs untreated control group rate of 30% (6/20)

General comments

- Generalisability: Inclusion and exclusion criteria were defined. Exclusion criteria: known pathology and recognisable causes of short stature excluded by clinical examination and screening tests (not specified). Low birth weight was not an exclusion criteria. No details were given of method used to select sample, which had narrow age band (small SD)
- Outcome measures: FH/NFH was not defined so not clear if the use of this measure is appropriate
- Intercentre variability: Number of centres not specified. Authors from one site
- Conflict of interests: Funding support from Kabi Pharmacia UK Ltd and AB Sweden

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 (no method)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 30% (12/41) GH-treated: 29% (6/21) Control: 30% (6/20)

Reference and design	Intervention	Patients	Outcome measures
Soliman & Abdul-Khadir, 1996[23] (Egypt) Study type/design: RCT after determination of GH status Jadad score: 2/5	Treatment arms: Group IIIa: GH, 15 U/m^2/week Group IIIb: untreated control (For groups Ia, Ib, IIa and IIb, see appendix 11) Length of treatment: 1 year. Other interventions used: not stated	Total number: 77 patients Group IIIa. GH, 15 U/m^2/week: 12 patients Group IIIb. Control: 12 patients (Groups Ia, Ib, IIa and IIb: 53 patients) Characteristics of target population: • < 3rd percentile in height • Prepubertal • Peak GH response to clonidine and insulin provocation was > 10 µg/l in group III Participants in Group III (mean ± SD): • Age: 7 ± 1.5 years • GV: 4.5 ± 1.6 cm/year • HtSDS: 2.8 ± 0.96 • BA: < 10 years Setting: outpatient clinic	Height GV HtSDS Circulating IGF-I, GH, thyroxine and TSH concentrations Oral glucose tolerance Length of follow-up: 0.96–1.04 years

Results (mean ± SD)

- GV (cm/year) before treatment: Group IIIa, 4.2 ± 0.9; Group IIIb, 4.5 ± 1.6
- GV (cm/year) after treatment: Group IIIa, 7.6 ± 1.2; Group IIIb, 5.5 ± 1.5. ($p < 0.05$ before and after for Group IIIa; $p < 0.05$ for Group IIIa vs IIIb)
- HtSDS before treatment: Group IIIa, –2.55 ± 0.5; Group IIIb, –2.8 ± 0.96
- HtSDS after treatment: Group IIIa, –1.7 ± 0.45; Group IIIb, –2.6 ± 0.9. ($p < 0.05$ before and after for Group IIIa; $p < 0.05$ for Group IIIa vs IIIb)
- Positive responders (GV ≥ 2 cm/year above pretreatment GV): Group IIIa, 9/12; Group IIIb, ?/12
- No adverse effects reported

Comments

Methodological comments

- Allocation to treatment groups: Random, method not stated
- Blinding: Not stated
- Comparability of treatment groups: No differences in baseline GV and HtSDS of patients and controls (no other baseline comparisons)
- Method of data analysis: Not ITT analysis. Data presented as mean ± SD. Paired Student's *t*-test used to analyse changes in each group before treatment and after 1 year. Simple linear regression was used to test correlation between variables. No point estimates with CIs given
- Sample size/power calculation: Not stated
- Attrition/drop-out: No withdrawals or drop-outs in Group III

General comments

- Generalisability: Inclusion and exclusion criteria defined. Exclusion criteria: reduced weight to height, systemic disease, history of head trauma or cranial irradiation, malnutrition, psychosocial dwarfism or hypothyroidism
- Outcome measures: Appropriate outcome measures used, but not FH. HtSDS calculated as (X1–X2) ÷ SD, where X2 and SD are age-matched population mean height and SD, and X1 is the patient height. Normal population data according to Tanner
- Group III ($n = 24$) part of larger trial with complicated design. Groups IIIa and IIIb comprised non-GH-deficient children. Group IIIa was treated with GH, and Group IIIb was control group
- Conflict of interests: Not stated

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Group III overall: 0

Reference and design	Intervention	Patients	Outcome measures
Barton *et al.*, 1995[40] (UK) RCT Jadad score: 2/5 (for 1 year)	Year 1: Observation Standard GH: 20 IU/m^2/week by daily s.c. injection (Genotropin) High GH: 40 IU/m^2/week by daily s.c. injection (Genotropin) Year 2: Observation group randomised to one of the two treatment groups. Other groups as year 1 Length of treatment: 2 years Other interventions used: none reported	Total number: 29 children (83% boys) Observation: 9 children (89% boys) Standard GH: 10 children (60% boys) High GH: 10 children (100% boys) Characteristics of target population: • Short prepubertal, normally growing children attending growth clinics • HtSDS: < –1.5 for age and sex • GVSDS: > –1.5 over preceding 12 months (TW standard) Participants, median (range) (values across the three groups given): • Age: 7.3–7.9 (5.1–9.5) years • BA delay: 0.0–0.6 (–1.8 to 2.3) years • HtSDS: –2.0 to –2.2 (–3.1 to –1.1) • GVSDS: –0.59 to –0.25 (–1.68 to 0.89) • Peak GH (mU/l): 12.6–15.6 (1.5–47.7) Setting: two tertiary referral centres	GV HtSDS/BA Cardiovascular effects (left ventricular mass index and left ventricular function) Biochemistry (IGF-I, plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood glucose and HbA_{1c}) Length of follow-up: 2 years

Results (ITT analysis for 1 year)

Baseline to 1 year, median (range):

- HtSDS: High GH group, from –2.0 (–2.7 to –1.1) to –1.2 (–1.9 to –0.4); standard GH group, from –2.1 (–3.1 to –1.7) to –1.7 (–2.8 to –1.0); observation group, from –2.2 (–3.1 to –1.5) to –2.1 (–3.3 to –1.2). No significant differences
- GVSDS: High GH group, from –0.25 to +5.66; standard GH group, from –0.59 to +2.71; observation group, from –0.45 to –0.48 (Kruskal–Wallis $H = 22.9$, $p < 0.001$)
- HtSDS/BA: High GH group, from –1.8 (–3.0 to 0.0) to –0.9 (–2.0 to 0.6); standard GH group, from –1.9 (–2.8 to –0.7) to –1.3 (–2.2 to –0.9); observation group, from –1.6 (–2.2 to 0.4) to –1.2 (–2.0 to 0.6). No significant differences
- ΔHtSDS/BA: High GH group, +1.1 (0.0 to +1.7); standard GH group, +0.4 (–0.3 to +0.9); observation group, +0.1 (–0.2 to +0.9) ($H = 6.3$, $p = 0.04$)
- ΔBA/ΔCA (skeletal maturation): Difference in ratio was not significantly different between GH-treated groups and the control group
- Adverse effects: Plasma total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides in GH-treated groups were not significantly different from controls after 1 year. Fasting blood glucose and HbA_{1c} were unchanged

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported
- Blinding: Echocardiographer was blinded. Otherwise no blinding was reported
- Comparability of treatment groups: Groups reported to be similar in growth and endocrine parameters. Appears to be difference in sex ratio between groups
- Method of data analysis: ITT analysis for 1-year data. Point estimates and CIs of differences between groups were not reported. Non-parametric ANOVA used (Kruskal–Wallis) and Mann–Whitney. Changes within groups over time analysed by Wilcoxon matched-pairs signed rank-sum test
- Sample size/power calculations: Small sample size may have lacked power to detect significant differences between groups. No power calculation
- Attrition/drop-out: None in year 1

General comments

- Generalisability: Inclusion and exclusion criteria were defined. Exclusion criteria: history of significant cardiovascular, respiratory or renal disease
- Outcome measures: Short-term study; FH was not reported
- Intercentre variability: Two centres were involved, but intercentre variability was not assessed
- Conflict of interests: Funding support from Children Nationwide and Pharmacia, Stockholm

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	1
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Overall: 0% (year 1)

Reference and design	Intervention	Patients	Outcome measures
Volta *et al.*, 1993[41] (Italy) Study type/design: RCT Jadad score: 1/5	Treatment arms: No treatment GH: 16 U/m^2/week in four s.c. injections (Genotropin) GH as above plus LHRHa (Suprefact): 1200 µg/day intranasally Length of treatment: 1 year Other interventions used: none reported	Total: 18 children (9 boys, 9 girls) Control: 6 children (3 boys, 3 girls) GH: 6 children (4 boys, 2 girls) GH + LHRHa: 6 children (2 boys, 4 girls) Characteristics of target population: • Pubertal children with familial short stature Participants: • Mean age: 11.9 ± 0.4 years (range, 10.4–13.7 years) • Genetic target < 10th percentile • Height < 3rd percentile • BA within 2 SD for CA • Height prognosis < 3rd percentile • Pubertal stage B2–3 for girls and G2–3 for boys (Tanner) • Normal GV for CA • Normal birth weight • Plasma GH levels after pharmacological stimulation > 10 ng/ml • Basal and LHRH-stimulated LH and FSH consistent with first stage of puberty Setting: growth clinic, two centres	Primary outcomes: HtSDS GV GVSDS related to BA Height prognosis SDS Secondary outcomes: Serum GH, thyroid function tests, LH, FSH, HbA_{1C} levels, BA Length of follow-up: treatment for 1 year

Results (ITT analysis)

Baseline to 1 year (mean ± SE):

- HtSDS: Untreated group, from –2.3 ± 0.2 to –2.2 ± 0.1; GH group, from –2.2 ± 0.2 to 1.7 ± 0.2 ($p < 0.05$); GH + LHRHa group, from –2.4 ± 0.3 to –2.3 ± 0.3. No differences between groups
- GV (cm/year): Untreated group, from 4.7 ± 0.4 to 6.6 ± 0.6 ($p < 0.05$); GH group, from 4.4 ± 0.3 to 8 ± 1 ($p < 0.05$); GH + LHRHa group, from 5 ± 0.5 to 6.5 ± 0.4
- GVSDS for BA: Untreated group, from –1.3 ± 0.2 to 0.4 ± 1 ($p < 0.05$); GH group, from –0.9 ± 0.5 to 3.9 ± 1.3 ($p < 0.05$); GH + LHRHa group, from –0.2 ± 0.7 to 0.3 ± 0.7. Value at 1 year in GH group significantly greater compared to untreated and GH + LHRHa groups, 3.9 ± 1.3 vs 0.4 ± 1 and 0.3 ± 0.7, respectively ($p < 0.05$)
- Height prognosis SDS: Untreated group, from –2.3 ± 0.3 to –2.4 ± 0.3; GH group, from –1.8 ± 0.3 to –1.0 ± 0.2 ($p < 0.05$); GH + LHRHa group, from –2.0 ± 0.3 to –2.4 ± 0.3. Value at 1 year in GH group significantly greater compared to untreated and GH + LHRHa groups, –1.0 ± 0.2 vs –2.4 ± 0.3 and –2.4 ± 0.3, respectively ($p < 0.05$)
- Regular pubertal progression observed in children in untreated and GH groups, with no progression in GH + LHRHa group, in accordance with LH and FSH suppression

Adverse effects: None reported

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported
- Blinding: None
- Comparability of treatment groups: Reports no differences present at baseline in auxological parameters (values presented in table). Sex distribution varies between groups
- Method of data analysis: Results presented as mean ± SE for all 18 children entered, so method seems to be ITT. Differences between groups reported in terms of statistical significance and point estimate, with no CI of differences given. Paired Student's *t*-test used for intragroup evaluations, and ANOVA corrected by Bonferroni for multiple comparisons among independent groups. Height prognosis determined using Bayley and Pinneau method
- Sample size/power calculations: Very small sample size and no prior power calculations
- Attrition/drop-out: No drop-outs

General comments

- Generalisability: Inclusion criteria broad. Exclusion criteria: dysmorphic syndromes, chronic disease. Good definition of characteristics of sample. Very small sample size limited power to detect differences. Differing sex ratios among groups
- Outcome measures: Appropriate outcomes, but no FH reported. Short-term study over 1 year
- Intercentre variability: Authors from two centres. No intercentre variability was assessed
- Conflict of interests: Funding support not mentioned

Quality assessment for RCTs (Jadad score)

Question	Score
Was the study described as randomised?	1 (no method)
Was the study described as double-blind?	0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	None

Reference and design	Intervention	Patients	Outcome measures
Cowell, 1990[42] (Australia and New Zealand) Multicentre RCT Jadad score: 2/5 (for first 6 months)	First 6 months: Placebo GH: 0.6 IU/kg/week (Genotropin) GH: 1.2 IU/kg/week (Genotropin) Second 6 months: All children received GH in either dose (no details) Length of treatment: 12 months Other interventions used: none reported	Total number: 104 children (83% boys) First 6 months: Placebo: 27 children GH (low dose): 37 children GH (high dose): 40 children Characteristics of target population: • Short, slow-growing children • Normal provocative GH secretion (peak GH > 20 mU/l) • 18% premature at birth Participants: • Mean CA: 9.7 years (range, 3.2–15.5 years) • BA: < 10 years in girls and < 12 years in boys • Mean HtSDS: –3 (range, –5.0 to –1.91) • Mean GV: 4.19 cm/year (range, 2.24–8.63 cm/year) • Mean GVSDS: –2.41 (range, –4.72 to –0.16) Setting: paediatric growth centres	GV IGF-I Length of follow-up: 12 months

Results (no ITT analysis)

First 6 months, mean ± SD:

- GV (cm/year): Placebo group, 5.3 ± 1.0; low-dose GH group, 8.7 ± 1.8; high-dose GH group, 10.8 ± 1.8. Significant difference in height velocity between groups (no *p*-value given. In placebo group, there was significant increase in GV (no *p*-values)
- Catch-up growth: Placebo group, 5/27 patients; low-dose GH group, 31/35 patients; high-dose GH group, 40/40 patients
- Adverse effects: Report states that no significant side-effects were observed

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation not reported. Stratification for patient numbers at each of eight centres
- Blinding: Described as double-blind. Treatment coded, so probably patients, health workers and study personnel were all blinded
- Comparability of treatment groups: No differences between randomised groups for pretreatment variables
- Method of data analysis: Analysis not on an ITT basis. Point estimates and CI of differences between treatment groups were not reported. Limited reporting of results. Wide age range may have included children undergoing puberty – no comment on influence of puberty on results
- Sample size/power calculations: No power calculation
- Attrition/drop-out: Not reported by treatment group. Reasons not given. Two children did not complete study

General comments

- Generalisability: Inclusion and exclusion criteria were defined. Exclusion criteria: recognisable dysmorphic/skeletal disorders. Wide age range (3.2–15.5 years)
- Outcome measures: Short-term study. FH not reported
- Intercentre variability: Not assessed. Eight different centres were involved
- Conflict of interests: Funding support from Kabi Peptide Hormones, Stockholm, Sweden

Quality assessment for RCTs (Jadad score) for first 6 months

Question	Score
Was the study described as randomised?	1 + 0
Was the study described as double-blind?	1 + 0
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	First 6 months: Overall: 2% (2/104) Not reported by treatment group

Reference and design	Intervention	Patients	Outcome measures
Ackland *et al.*, 1990[43] (UK) RCT Jadad score: 3/5 (for first 6 months for 58 children, Groups A and B)	First 6 months: Group A: placebo by s.c. injection, 3 times per week Group B: GH, 0.27 IU/kg (0.1 mg/kg), 3 times per week by s.c. injection. (Humatrope) Group C: observation Second 6 months: All groups received GH in above dose Third 6 months: GH stopped. All observed Length of treatment: maximum of 1 year Other interventions used: none reported	Total: 95 children (77% boys) Numbers per treatment group were not reported Characteristics of target population: • Short children • Height: ≤ 3rd percentile (TW standard) • Age: > 5 years • Prepubertal • Normal birth weight for gestational age • GH response to pharmacological testing > 15 mU/l Participants: • Mean age: 9.7 years (range, 5–14.2 years) • Mean HtSDS: –2.7 (range, –4.2 to –1.6) • Mean GVSDS over previous year: –1.2 (range, –3.0 to +1.1) Setting: not specified	Physiological GH secretion GVSDS Epiphyseal maturation (BA using TW2-RUS method) Length of follow-up: 18 months

Results (mean ± SD)

Baseline to 6 months (placebo group, n = 28; GH group, n = 30; observation group, n = 31):

- GVSDS: Placebo group, from –1.29 to –0.63 (p = 0.03); GH group, from –1.26 to +1.98 (p < 0.0001); observation group, from –1.09 to –0.87 (NS, p > 0.05). GH group vs placebo group, p < 0.0001. No significant difference between placebo and observation group

Second 6 months (all on GH):

- GVSDS: Placebo group, from –0.63 to +2.03 (p < 0.0001); GH group, from 1.98 to 1.09 (p = 0.0005); observation group, from –0.87 to +1.81 (p < 0.0001). Growth rates did not differ significantly between groups. GVSDS of Group B decreased

Third 6 months (GH stopped):

- GVSDS: Individual groups all showed significant fall (p < 0.0001). Placebo group, from 2.03 to –0.71; GH group, from 1.09 to –1.16; observation group, from 1.81 to – 0.34
- Epiphyseal maturation: No difference between treatment groups. Mean delay in BA at entry was 1.12 ± 1.21 years, compared to 1.0 year after 18 months (n = 31)

Adverse effects: not reported

Comments

Methodological comments

- Allocation to treatment groups: Method of randomisation was not reported
- Blinding: During first 6 months, two groups were in double-blind RCT (patients and health workers). Not clear if those assessing outcomes were blinded
- Comparability of treatment groups: Groups comparable at baseline on age, HtSDS and height velocity SDS (data not presented)
- Method of data analysis: Number of patients included in the analysis was reported only for first 6 months. There were 89 of 95 patients evaluated, therefore does not appear to be ITT analysis. Point estimates and CIs/SDs were not reported. Statistical analysis used Pearson product-moment correlation coefficients and t-tests (paired and unpaired) for within and between-group comparison. Repeat profiles assessed using Wilcoxon signed rank test
- Sample size/power calculations: No power calculations
- Attrition/drop-out: Not reported. Results described for 89 patients

General comments

- Generalisability: Inclusion and exclusion criteria were clearly defined. Exclusion criteria: chronic disease/dysmorphic syndromes and TS
- Outcome measures: RCT was short term (6 months). FH was not reported. Focused on GH secretion
- Intercentre variability: Number of centres taking part was not reported
- Conflict of interests: Funding support from Eli Lilly and Adint Trust

Quality assessment for RCTs (Jadad score) first 6 months

Question	Score
Was the study described as randomised?	1 (no method)
Was the study described as double-blind?	1 + 1 (method given) only for 58 children in Groups A and B
Was there a description of withdrawals and drop-outs?	0
What proportion of sample (intervention and control groups separately) withdrew or dropped out?	Drop-outs: 6% (6/95) Not reported by group 95 patients entered, 89 analysed

LH, luteinising hormone; FSH, follicle-stimulating hormone; SE, standard error

Appendix 20

Summary of evidence of effectiveness of GH in ISS: non-RCTs reporting final height

Reference and design	Intervention	Patients	Outcome measures
Zadik *et al.*, 1992[53] (Israel) Study type/design: non-RCT	Treatment arms: GH: 0.75 U/kg/week in three doses for 2 years, followed by weekly dose divided into seven daily doses until FH reached (Biotropin) Untreated control Length of treatment: until FH (range, 6–16 years) Other interventions used: not stated	Total number: 28 boys GH group: 11 boys Untreated controls: 17 boys Characteristics of target population: • ISS (< 2 HtSDS for age) • Subnormal IC-GH (< 3.2 µg/l) • Peak GH level after stimulation: > 10 µg/l • GV: < 4.5 cm/year • BA retardation: > 2 SD for age • Born at full term and normal birth weight for gestational age Participants: Control group: • CA: 12.5 ± 1.7 years • BA/CA: 0.8 ± 0.1 • HtSDS: –3.1 ± 0.9 • GVSDS: –2.8 ± 1.2 • Target height: 162.5 ± 5.9 cm; SDS, –1.9 ± 0.9 • Predicted height: 161.8 ± 5.9 cm; SDS, –1.8 ± 1.0 GH group: • CA: 12.8 ± 1.3 years • BA/CA: 0.75 ± 0.1 • HtSDS: –3.3 ± 0.9 • GVSDS: –2.4 ± 0.95 • Target height: 159.6 ± 4.5 cm; SDS, –2.1 ± 0.5 • Predicted height: 162.1 ± 7.6 cm; SDS, –1.8 ± 0.8 Setting: hospital growth clinic	Primary outcome measure: FH Secondary outcome measures: GV IGF-I levels Puberty onset Puberty duration Height at onset of puberty Prepubertal height gain Height gain during puberty Length of follow-up: until FH attained (maximum of 16 years)

Results (mean ± SD)

- FH: GH group, 164.5 ± 3.9 cm; untreated group, 157.6 ± 4.5 cm ($p < 0.04$)
- Final HtSDS: GH group, –1.5 ± 0.6; untreated group, –2.7 ± 0.7 ($p < 0.04$)
- GV (cm/year):
  Pretreatment: GH group, 3.5 ± 0.9; untreated group, 3.3 ± 0.6
  Year 1: GH group, 9.3 ± 2.1; untreated group, 5.3 ± 1.1 ($p < 0.01$)
  Year 2: GH group, 8.6 ± 2.3; untreated group, 6.8 ± 1.7 ($p < 0.01$)
  Year 3: GH group, 6.2 ± 1.9; untreated group, 6.3 ± 2.0
  Year 4: GH group, 5.4 ± 3.8; untreated group, 6.2 ± 3.6
  Year 5: GH group, 0.3 ± 0.5; untreated group, 1.5 ± 2.0
- GV: Velocity in treated group was significantly higher than that of untreated group over years 1–5 (repeated measure ANOVA, $F(1, 30) = 13.5$, $p = 0.001$)
- Change in HtSDS: GH group, baseline –3.1 ± 0.9, final –1.5 ± 0.6; untreated group, baseline –3.3 ± 0.9, final 2.7 ± 0.7
- Prepubertal height gain: GH group, 8.7 ± 4.0 cm; untreated group, 5.6 ± 2.0 cm
- Pubertal height gain: GH group, 19.27 ± 4.0 cm; untreated group, 19.0 ± 2.2 cm
- Adverse effects: Not reported

continued

Comments

Methodological comments

- Allocation to treatment groups: Patients randomly offered GH therapy (no details)
- Blinding: Not stated
- Comparability of treatment groups: Groups appear similar at baseline
- Method of data analysis: Appropriate. FH: change in height gain < 0.5 cm in 6 months and skeletal epiphyseal fusion. PAH determined using Bayley and Pinneau method. Target height: sex-corrected mid-parental height expressed as SDS units. BA determined using Greulich and Pyle method
- Sample size/power calculation: None reported
- Attrition/drop-out: Not reported

General comments

- Generalisability: Boys mostly from families with short stature. Inclusion criteria were defined. Exclusion criteria: chronic disease and dysmorphic syndromes. No details of sample selection
- Outcome measures: Appropriate but excluded adverse reactions. Outcomes were defined
- Conflict of interests: Not stated

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment		✗				Method not clear
Proper sampling		✗				
Adequate sample size				✗		Small sample size
Objective outcomes	✗					
Blind assessment			✗			
Objective eligibility criteria	✗					
Reported attrition			✗			
Comparability of groups	✗					
Generalisability		✗				No details of method of sampling

Reference and design	Intervention	Patients	Outcome measures
Hindmarsh & Brook, 1996[54] (UK) Study type/design: Open non-RCT	Treatment arms: GH: In year 1, 2 U s.c. nightly for six nights per week (dose range, 12.2–21.0 U/m^2/week) In year 2, randomised to 20 U/m^2/week or continued on same dose After end of year 2, all received 20 U/m^2/week in daily s.c. injections Untreated control Length of treatment: median of 7.5 years (range, 4–9 years) Other interventions used: not stated	Total number: 26 children GH group: 16 children Controls: 10 children Characteristics of target population: • Short children with normal pretreatment growth rates and normal responses to physiological and pharmacological testing Participants: GH group: • Mean age: 8.35 ± 1.88 years • Sex: 10 boys, 6 girls • HtSDS/CA: –2.17 ± 0.58 • HtSDS/BA: –0.95 ± 1.03 • GVSDS: –0.44 ± 0.33 • Target HtSDS: –0.88 ± 1.00 • Pretreatment predicted HtSDS: –1.75 ± 0.71 • Peak GH response to ITT: 27.9 ± 0.2 mU/l Control group: • Mean age 7.62 ± 1.50 years • Sex: 6 boys, 1 girl • HtSDS/CA: –2.34 ± 0.61 • HtSDS/BA: –0.96 ± 0.72 • GVSDS: –0.36 ± 0.28 • Target HtSDS: –0.29 ± 0.61 • Pretreatment predicted HtSDS: –2.04 ± 0.58 • Peak GH response to ITT: 28.2 ± 6.8 mU/l Setting: growth disorder clinic	Primary outcome measure: FH Secondary outcome measures: Change with time in predicted HtSDS Factors associated with final HtSDS Length of follow-up: median of 7.5 years (range, 4–9 years)

Results (mean ± SD)

- FH: Not given. GH group, average increment of +2.8 cm for boys and +2.5 cm for girls
- Predicted HtSDS to final HtSDS: GH group, from –1.75 ± 0.71 to –1.33 ± 0.94 (p = 0.03). Change of +0.42 ± 0.79 represents average increment as above. Untreated control group, from –2.04 ± 0.58 to –1.88 ± 0.57 (not significant change of 0.16 ± 0.2)
- Adverse effects: Triceps and subscapular skinfold thickness decreased significantly during first 6 months of treatment, but there were no significant differences thereafter. No change in basal or 120-minute stimulated blood glucose concentrations during first 2 years of therapy. No significant change in systolic or diastolic blood pressure

Comments

Methodological comments

- Allocation to treatment groups: Not randomised
- Blinding: Measurement of children and assessment of BA were done by assessor blinded to treatment
- Comparability of treatment groups: No significant differences in anthropometric status between groups at start
- Method of data analysis: Not ITT. One of the 16 children entered had not attained FH, and predicted FH was substituted
- Sample size/power calculation: Estimates that using sample size of 16 patients can detect change of 3.2 cm with significance level of 5% and 95% power. Small sample size
- Attrition/drop-out: Three out of 10 patients in the observation group dropped out

General comments

- Generalisability: Consecutive referrals were enrolled, so sample likely to be representative
- Outcome measures: Measures were appropriate and included monitoring for adverse effects; actual FH and GV were not reported. FH: no growth or GV < 0.5 cm/year with adult bone maturation. BA: Tanner–Whitehouse mark 2. HtSDS: Tanner 1966. Predicted height: Tanner–Whitehouse mark 2
- Conflict of interests: rhGH supplied by Pharmacia & Upjohn

continued

Quality assessment (revised from Spitzer* et al.*, 1990)[11]

	Yes	Uncertain/ incomplete/ substandard	No	Don't know/ not reported	Not applicable	Comments
Proper random assignment			✗			
Proper sampling	✗					
Adequate sample size			✗			No *a priori* power estimate; power of sample size was estimate
Objective outcomes	✗					
Blind assessment	✗					BA blinding assessed
Objective eligibility criteria		✗				Reported in detail elsewhere
Reported attrition	✗					Drop-outs 3/26 (12%)
Comparability of groups	✗					Except control group declined to participate
Generalisability	✗					Consecutive referrals

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We look forward to hearing from you.

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