Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

***Final Protocol (September 2008*)**

1. Title of the project

Human growth hormone in children

2. Plain English Summary

One of the factors essential for a child's growth is production of an adequate level of natural growth hormone by the pituitary gland at the base of the brain. Human growth hormone (HGH), also called somatropin, is licensed to treat children who have restricted growth due to a range of medical conditions. Children with growth hormone deficiency (GHD) do not produce enough of this hormone naturally, so injections of a synthetic form can help to increase their growth rates. Children with Prader-Willi syndrome (PWS) are characteristically of short stature and have altered body composition. They may also be growth hormone deficient, so treatment with growth hormone can be used to replace natural levels of the hormone for these patients. Treatment with HGH is primarily used to improve body composition and metabolism in children with PWS.

Short stature is also a common feature in children with other conditions such as Turner syndrome (TS); chronic renal insufficiency (CRI); children born small for gestational age (SGA) or with short stature homeobox-containing gene (SHOX) deficiency. Children with these conditions may have reduced sensitivity to normal levels of GH, so supplementary injections of synthetic growth hormone may help to increase their growth rates.

This review will systematically summarise the results of clinical trials which evaluate the use of human growth hormone for the treatment of children with GHD, TS, CRI (prepubertal children only), PWS, and those born SGA or with growth failure associated with SHOX deficiency confirmed by DNA analysis. The report will include a systematic review of cost effectiveness studies and an economic evaluation, to give an indication of the cost-effectiveness of HGH for the NHS in England and Wales.

3. Decision problem

Recombinant human growth hormone (somatropin) is currently recommended by NICE[1] for children with a proven clinical diagnosis of GHD, TS or PWS and for pre-pubertal children with CRI. Since the last review, somatropin has received marketing authorisation for the treatment of children born SGA and for children with growth failure associated with SHOX deficiency. The review will update

and extend the existing systematic review[2] with any new evidence for the use of growth hormone for children with GHD, TS, PWS or CRI. In addition, evidence for the use of human growth hormone for children born small for gestational age, or with SHOX deficiency (conditions not considered in the original review) will be included in this report.

3.1 Background

3.1.1 Growth hormone deficiency

Growth hormone deficiency occurs when the pituitary gland fails to produce sufficient levels of growth hormone. It can be caused by a variety of factors, but in many cases the cause is unknown (idiopathic GHD). In some children, failure or reduction in growth hormone secretion is congenital, and may be accompanied by other pituitary hormone deficiencies. Other children have genetic mutations such as GH-1 gene mutation (which leads to isolated GHD) or PROP-1 gene mutations which may lead to multiple hormone deficiency including GHD. In others, growth hormone deficiency is acquired as a result of: trauma, either at birth or later in childhood; infiltration from histiocytosis, lymphoma or leukaemia; pituitary or hypothalamic tumours; or following radiotherapy.[2] The diagnosis of GHD includes a height of more than 3 SD below the mean, a height velocity more than 2SD below the mean for a year or a height velocity of more than 1.5 SD below the mean for two years.[3] Untreated patients have a final height of 134-146cm in males and 128-134 cm in females.[4] People with GHD are also at greater risk of cardiovascular disease if they develop an adverse lipid profile.

The UK Child Growth Foundation estimates that idiopathic GHD occurs in about one in every 3800 births,[5] but reliable figures are difficult to obtain for GHD associated with radiotherapy and other causes. The true incidence may also be higher when difficult to diagnose, borderline cases are taken into account. An increasing number of children are surviving childhood cancers as treatments improve, and consequently require treatment with GH to overcome associated GHD. Treatment with GH is currently recommended by NICE to help increase the growth of children with GHD.[1]

3.1.2 Turner syndrome

Turner syndrome is characterised by the complete or partial absence of the second sex chromosome in girls, sometimes with cell populations which differ in genetic make up (cell line mosaicism),[6] in addition to the presence of characteristic physical features.[7;8] The condition affects approximately one in 2500 live-born females.[9;10] In the majority of girls with TS, the missing or abnormal second chromosome causes ovarian failure, preventing sexual maturity. Girls with TS therefore receive oestrogen replacement therapy as part of their treatment. Not all girls with TS will require GH treatment and the condition does not involve a deficiency in natural growth hormone secretion,

although there may be a relative lack of sensitivity to GH.[2] The average adult height deficit of 20cm in women with TS is mostly due to haploinsufficiency of the SHOX gene.[11] Treatment with GH is currently recommended by NICE to help boost the growth of girls with TS.[1]

3.1.3 Growth disturbance in children born SGA

There are various thresholds for defining a child as being born SGA, but the European license is for children whose height is less than -2.5 SD (0.4th centile), which would give an incidence of 0.4% of children who would fall below this level. More than 80% of babies born SGA will achieve catch-up growth (growth velocity greater than the median for chronologic age and gender[12]) during their first six months.[13], with catch-up growth completed within two years for most SGA infants.[14;15] However, babies born prematurely who are SGA may take around four years to achieve catch-up growth.[16]

It has been estimated that approximately 10% of SGA children remain at a height below -2SD throughout their childhood.[17;18] Children who are born SGA with low birth weight and who do not achieve catch-up growth by the age of two years face a relative risk of short stature < -2SD at age eighteen of 5.2. For SGA children with low birth length the relative risk is 7.1.[15]

Published estimates of the annual incidence of SGA births in Sweden and the Netherlands vary between 3%[17;19] and 5.4%.[20] A 2005 audit by the British Society for Paediatric Endocrinology and Diabetes found 205 patients with a diagnosis of SGA being treated with GH in the UK.[21]
There are several possible causes for children being born SGA. These include maternal factors, such as age, parity, medical conditions, smoking, malnutrition, and alcohol abuse; placental factors, and foetal factors such as chromosomal abnormalities and genetic defects.[12] Diagnosis of SGA can be complicated, requiring accurate knowledge of gestational age. Children classified as SGA may have concurrent diagnoses, such as familial short stature, TS, GHD or skeletal dysplasia.[12] Previous NICE guidelines did not consider children born SGA, as somatropin was not licensed for this indication at the time.[1] Its European license is for children aged four years and over.

3.1.4 Prader-Willi syndrome

Prader Willi syndrome is a genetic disorder, caused by an abnormality of chromosome 15. It is characterised by hyperphagia, hypogonadism, short final stature, dysmorphic features, hypoventilation, behavioural problems and a high risk of obesity.[22] Children with this syndrome often have reduced GH secretion, but this may be linked with obesity. A UK study carried out between 1998 and 2000 found an overall population rate of 1:52,000, considered to be the lower bound, with rates varying from 1:42,000 to 1:67,000 for individual counties.[23] This study also gave a birth incidence of 1:20,000, with a lower bound of 1:29,000. The same study found an overall death

rate for the PWS population (from the age of 3.4 to 56 years) of around 3% per year, which is higher than the standard death rate of about 0.3% each year for people up to the age of 55 years in England and Wales.[23] Mean final height for people with PWS is approximately 154cm in males and 145-149cm in females.[2] Treatment with GH is currently recommended by NICE to help increase the growth of children with PWS, and to help improve body composition.[1]

3.1.5 Chronic renal insufficiency

Chronic renal insufficiency (also known as chronic renal failure) is defined as a persistent elevation of serum creatinine and/or urea level. It can be caused by a variety of conditions, including congenital disorders, glomerular disorders and infections. Patients undergoing haemodialysis or peritoneal dialysis can be considered for GH treatment, as well as those who have received kidney transplantations. Growth failure associated with CRI can be caused by acidosis, rickets, GH resistance, inadequate nutrition and anorexia.[24] Children with CRI experience impaired growth once their glomerular filtration rate (GFR) falls to 50% of normal, with increasing problems once the GFR falls below 25%.[25] Following kidney transplantation, chronic graft rejection and treatment with steroids can restrict growth and development.[26]

The UK Renal Registry reported that there were 748 patients under the age of 18 years who were on renal replacement therapy in the UK's 13 paediatric renal centres.[27] An Italian study of the epidemiology of chronic renal failure in children found a mean incidence of 12.1 cases per million (range: 8.8–13.9), with a point prevalence of 74.7 per million of the age-related population.[28] Disney and colleagues give a prevalence of 32 per million children under the age of 15 in Australia and New Zealand having chronic kidney disease, defined by the need for dialysis or kidney transplant.[29]

Children with congenital disorders (approximately 60% of children with CRI)[26] are usually of normal length at birth, but are below the 3rd percentile for height within their first year and remain parallel to normal percentiles throughout childhood.[26] One study reported a mean height from birth to age ten which was -2.37 SD ± 1.6.[26] Similarly, final height is reported to be reduced to below the third percentile in patients who developed end-stage renal failure in childhood.[26] Adult final height was more than two standard deviations below the mean for approximately 60% of boys and 41% of girls who started renal replacement therapy before they were 15 years old.[30]

Treatment with GH is currently recommended by NICE to help increase the growth of prepubertal children with CRI, when nutritional status.[1] GH treatment should be stopped after a renal transplantation, and only re-established after one year if it has been ascertained that catch-up growth has not occurred.[1]

3.1.6 SHOX deficiency

The short stature homeobox-containing gene (SHOX) is located on the distal ends of the X and Y chromosomes. This gene plays a significant role in long bone growth, and normal growth requires two functional copies.[31;32] Growth impairment can result from having only a single functional copy of the SHOX gene, with the other inactivated by mutation (haploinsufficiency), or deletion.[31] SHOX deficiency can cause short stature in a range of medical conditions. Clinical features associated with SHOX deficiency include disproportionate shortening of the middle sections of the limbs, bowing of the forearms and lower legs and arm-bone abnormality[31] SHOX deficiency can cause short stature in people with concurrent diagnoses such as Turner syndrome or idiopathic short stature. One study estimated a prevalence of SHOX deficiency of at least 1 in 2000 children.[33]

3.2 Definition of the intervention

Recombinant human GH (somatropin) has been available since 1985, following the withdrawal of cadaveric human pituitary GH due to possible transmission of Creutzfeldt-Jakob disease.[2] Somatropin is a synthetic form of human growth hormone produced by recombinant DNA technology, having a sequence identical to that of pituitary-derived human growth hormone. Licensed dosages vary for the different indications (Table 1), depending on whether the treatment is aiming to replace growth hormone to normal levels (for children with growth hormone deficiency), or being used in supraphysiological doses where there is no hormone deficiency but some lack of sensitivity to the hormone. It is given as a subcutaneous injection, usually at night (to mimic the child's natural fluctuations in growth hormone).[2] Seven pharmaceutical companies have UK marketing authorisations for various indications, as shown in Table 1.

Table 1 Indications for the use of somatropin in children

Indication	**Dose***	**Licensed drugs (manufacturers)**
Growth hormone deficiency	23-39 micrograms/kg daily, or 0.7-1.0 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) Zomacton (Ferring Pharmaceuticals UK) NutropinAq (Ipsen Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
Turner's syndrome	45-50 micrograms/kg daily, or 1.4 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) Zomacton (Ferring Pharmaceuticals UK) NutropinAq (Ipsen Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
Growth disturbance (current height SDS -2.5 and parental adjusted height SDS, -1) in short children	35 micrograms/kg daily, or 1.0	Humatrope (Eli Lilly & Co. Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd)

born SGA, with a birth weight and /or length below -2SD, who failed to show catch up growth (HV SDS<0 during the last year) by 4 years of age or later	mg/m^2 daily	Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
Prader-Willi syndrome, with growth velocity > 1cm/year (in combination with energy-restricted diet)	35 micrograms/kg daily, or 1.0 mg/m^2 daily; max 2.7 mg daily.	Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd)
Chronic renal insufficiency in children (renal function decreased to < 50%)	45-50 micrograms/kg daily, or 1.4 mg/m^2 daily	Humatrope (Eli Lilly & Co. Ltd) NutropinAq (Ipsen Ltd) Norditropin Simple Xx (Novo Nordisk Ltd) Genotropin (Pfizer Ltd) Omnitrope (Sandoz Ltd) Saizen (Merck Serono)
SHOX deficiency	0.045-0.050mg/kg daily	Humatrope (Eli Lilly & Co. Ltd)

*Dosing information from the Electronic Medicines Compendium (http://emc.medicines.org.uk/), accessed 30 April 2008.

3.3 Place of the intervention in the treatment pathway

Growth hormone's place in the treatment pathway depends on the child's particular condition or syndrome, and age at diagnosis. Appropriate timing of treatment with growth hormone will depend on the underlying pathology.

- For children with congenital GHD, GH therapy is not generally started before the child is four years old.[2] However, if there is profound growth failure or evidence of recurrent hypoglycaemia, which may occur in infants under the age of one, treatment may be started earlier. For children who acquire GHD at an older age, treatment can start at a time appropriate to their condition and stage of growth. GH therapy is contraindicated in cases of progressive tumour activity and should not be used for growth promotion in children with closed epiphyses.
- Treatment would be discontinued after the first year if there is a poor response, i.e. <50% increase in growth rate, or if compliance or growth rate remains poor thereafter. Otherwise treatment could continue until height velocity was <2cm/year, assessed over 6-12 months, or once final height was achieved. Other clinical advice suggests that treatment is necessary for the patient to attain peak bone mass, which may not be until the age of 25 or 26 in some people. Standard practice would be to transfer the patient to the care of adult endocrinologists, to stop growth hormone treatment and perform dynamic function tests so see if the patient is still growth hormone deficient.
- Current NICE guidance recommends that GH treatment for girls with TS should begin at the earliest age possible.[1] Since height velocity generally reduces from 3-4 years of age, patients

diagnosed early will commence treatment around that age. Some patients with profound growth retardation and failure to thrive may commence treatment earlier. Clinical expert advice suggests that the mean age for starting treatment is 8-9 years of age as many girls are not diagnosed until later in childhood.

- The place of GH in the treatment pathway for children with CRF will depend on age at diagnosis, and on clinical factors related to management of the child's condition. GH treatment can take place either before or after renal transplant, although allograft rejection can be a concern if GH treatment is given post-transplant. GH therapy should not be used after renal transplant in seriously ill children.
- For children with PWS, treatment with GH is primarily intended to improve body composition and metabolism, but also to increase final height. Its place in the treatment pathway will depend on age at diagnosis, and a GH provocation test would be used to confirm whether the child is deficient in GH. Children with PWS are assessed for obesity, potential for obstructive sleep apnoea and ongoing respiratory illness before treatment is considered. Low muscle tone and its impact on the child's development are also considered.
- GH's place in the treatment pathway for children with SHOX deficiency will depend on age at diagnosis. Clinical evaluation would be used to assess growth failure, but there would be no need for GH provocation tests as SHOX deficiency would have been established.
- Children born SGA but with no comorbidities may not be diagnosed until they fail to achieve catch-up height within -2.5 SD by the age of two to four years,[12] or when they start school. The European license for HGH is for children aged 4 years and over.

3.4 Relevant comparators

The standard comparator for this review will be management strategies without somatropin.

3.5 Population and relevant sub-groups

The rationale for the initiation of growth hormone treatment in children is to maximise height potential and body composition. The relevant populations for this review are children with the following conditions:

- GHD;
- TS;
- CRI;
- PWS;
- SGA;
- SHOX deficiency.

Possible subgroups would be children with different causes of GHD, and children with CRI who are either pre- or post-transplant. However, analysis of the effectiveness of GH treatment for any of these subgroups of patients will be limited by the available data and the statistical power of any identified trials.

Transition of care from paediatric to adult endocrine services of young people whose linear growth is not complete requires patients to have repeat testing of their growth hormone axis to be sure that they need to continue treatment. This transition period will only be considered within this appraisal where evidence from the included studies allows.

3.6 Outcomes

Clinical outcomes will include: final height gained; height standard deviation score; growth velocity; growth velocity standard deviation score; body composition, and biochemical/metabolic markers as appropriate; adverse effects of treatment; health-related quality of life. Direct costs will include estimates of all health care resources consumed in the provision of the intervention, including diagnostic tests, administration and monitoring costs – as well as consequences of those interventions, such as treatment of adverse effects.

The scope for this project requires assessment of body composition for all indications, rather than only for PWS as in the previous review. Consequently, searches carried out for the previous review may not be extensive enough, and there will be an element of duplicating work in this area rather than a simple update for these conditions. Assessment of the clinical effectiveness of growth hormone will therefore be restricted to evidence from RCTs.

4. Report methods for synthesis of evidence of clinical and cost effectiveness

A review of the evidence for the clinical and cost effectiveness of somatropin will be undertaken systematically following standard guidelines from the NHS Centre for Reviews and Dissemination (CRD).[34] An expert advisory group of clinical experts and service users where appropriate will support the review team at key stages of the project.

4.1 Search strategy

- A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify studies reporting clinical-effectiveness, cost-effectiveness, health-related quality of life, resource use and costs, epidemiology and natural history.
- The draft clinical effectiveness search strategy for Medline is shown in Appendix 1. This will be adapted for other databases.

- A number of electronic databases will be searched including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); Medline (Ovid); Embase (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Bibliographies of related papers will be assessed for relevant studies where possible.
- The manufacturers' submissions to NICE will be assessed for any additional studies which meet the inclusion criteria.
- Experts will be contacted to identify additional published and unpublished references.
- Searches will be carried out from the inception date of the database. Although this will involve duplication of searches carried out for the previous review, it will be necessary to identify trials reporting body composition as an outcome measure, as these may not have been identified for all conditions in the previous review. For databases of abstracts and conference presentations searches will only be carried out for the past two years to capture any research that has not yet been fully published. All searches will be limited to the English language, and will be updated around February 2009.

4.2 Inclusion and exclusion criteria

4.2.1 Patients

Children with growth disturbance, as per licensed indication for each preparation available.

4.2.2 Interventions

Recombinant human growth hormone (somatropin)

4.2.3 Comparators

Treatment strategies without somatropin

4.2.4 Outcomes

The following outcomes will be included, where data are available:

- Final height gained
- Height standard deviation score
- Growth velocity
- Growth velocity standard deviation score
- Body composition, and biochemical/metabolic markers as appropriate
- Adverse effects of treatment
- Health-related quality of life

4.2.5 Types of studies

- Fully published randomised controlled trials (RCTs) or systematic reviews of RCTs will be included. Indicators of a systematic review include: explicit search strategy, inclusion criteria, data extraction and assessment of quality. Where we judge it necessary and appropriate, we will consider the inclusion of evidence from other non-randomised studies. Full economic evaluations (cost-effectiveness studies, cost-utility studies, cost-benefit studies) and reviews of economic evaluations will be included in the review of cost effectiveness.
- Studies published only as abstracts or conference presentations will only be included in the primary analysis of clinical and cost-effectiveness if sufficient details are presented to allow an appraisal of the methodology and assessment of results.
- Non-English language studies will be excluded.

4.3 Inclusion and data extraction process

- Two reviewers will assess the titles and abstracts of studies identified by the search strategy for potential eligibility.
- The full text of relevant papers will be requested for further assessment, and these will be screened independently by two reviewers.
- Data will be extracted by one reviewer using a standard data extraction form (Appendix 2) and checked by a second reviewer.
- At each stage, any discrepancy will be resolved by discussion, with involvement of a third reviewer where necessary.

4.4 Quality assessment

- The quality of included clinical effectiveness studies will be assessed using NHS CRD (University of York) criteria. The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the International consensus-developed list of criteria developed by Evers and colleagues,[35] and Drummond and colleagues.[36] For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues).[37]
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with differences in opinion resolved by discussion and involvement of a third reviewer where necessary.

4.5 Methods of analysis/synthesis

- Clinical- and cost-effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quality and homogeneity, a meta-analysis of the clinical-effectiveness studies will be performed, using appropriate software.
- Quality of life studies will be synthesised using the same methods as above, i.e. narrative review and meta-analysis as appropriate.

5. SHTAC economic model

5.1. Evidence to support economic model

Additional searches for other evidence to inform cost effective modelling will be conducted where necessary. Evidence may be drawn from a range of sources, including non-randomised controlled trials. Studies may be required which:

- assess HRQoL and the relationship between final height and mortality and morbidity rates in the different conditions;
- estimate utility based on HRQoL measures; or
- show a relationship between height and utility in adults.

5.2 Economic Modelling

Where appropriate, evidence from a variety of sources will be synthesised within an economic model. This will build upon earlier work (Bryant et al, 2002)[2] and also upon any relevant models found in the literature. This previous work adopted a cost per cm of final height approach and the duration of the model was until this final height was obtained. For the current analysis we will adopt a cost per QALY approach where feasible. This will entail constructing lifetime models for individuals and will require data on the relationship between the effects of successful treatment (to include but not necessary to be limited to increases in final height) and utility scores. If no data can be found to enable this approach we will adopt a cost per cm of final height approach as for the previous work (Bryant et al, 2002). For conditions not included in previous work, new models will be built if appropriate data is found. For conditions where the principle driver of quality of life is expected to be changes in final height we will use a common modelling framework. However, data values for various parameters would be expected to differ between these models. The process will be dependent on the identification of sufficient data to derive these models. The perspective will be that of the NHS and Personal Social Services. Both cost and outcomes (QALYs) will be discounted at 3.5%.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- The biological disease process (i.e. knowledge of the natural history of the disease);
- The main care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest); and
- The disease states or events which are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.
- Mortality / life expectancy for different conditions

A decision analytic model is most likely to be constructed in EXCEL. Parameter values will be obtained from relevant research literature, including our own systematic review of clinical and cost effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group we may use data from lower quality evidence sources, sponsor submissions to NICE or expert clinical opinion. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources, or from sponsor submissions to NICE, as appropriate.

Outcomes, in terms of final height, will be obtained from our own systematic reviews of clinical outcomes, or extrapolated from intermediary evidence. To capture health-related quality of life effects, utility values will be sought from the relevant research literature and from the manufacturers (via NICE). If a cost-utility approach is possible then the time frame used will be the patient's lifetime to reflect the chronic nature of these conditions and the fact that many potential gains from successful therapy could last for the entire duration of an individual's life. Alternatively, if a cost utility approach is not possible, the reasons for choosing an alternative (cost-effectiveness) approach will be clearly specified and justified, and the implications of this discussed.

Uncertainty will be explored through one-way sensitivity analysis and scenario analysis. Sensitivity analysis will also be used to test any assumptions used to derive cost and outcomes data. If the data and modelling approach permit we will explore uncertainty by the use of a probabilistic sensitivity analysis (PSA). The outputs of any PSA will be presented using plots of the cost-effectiveness plane and cost-effectiveness acceptability curves.

6. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 2nd March 2009. Data arriving after this date will not be considered. If the data meet the

inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided they comply with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission will be underlined in the assessment report, and highlighted in blue (followed by an indication of the relevant company name in brackets unless it is obvious from the context).

7. Competing interests of authors

None

8. Appendices

9.1. Draft search strategy

9.2. Data extraction form

Appendix 1 Draft search strategy for MEDLINE

1 growth disorders/
2 growth failure.ti,ab.
3 growth deficien*.ti,ab.
4 Prader-Willi Syndrome/
5 prader-willi.ti,ab.
6 turner syndrome/
7 (Turner*2 adj syndrome).ti,ab.
8 growth hormone deficien*.ti,ab.
9 GH deficien*.ti,ab.
10 GHD.ti,ab.
11 exp renal insufficiency chronic/
12 (chronic adj2 (renal or kidney*) adj2 (failure or insufficien*)).ti,ab.
13 (CRI or CRF).ti,ab.
14 "small for gestational age".ti,ab.
15 "short for gestational age".ti,ab.
16 infant small for gestational age/
17 "short stature homeobox-containing gene".ti,ab.
18 "short stature homeobox".ti,ab.
19 SGA.ti,ab.
20 SHOX.ti,ab.
21 PHOG.ti,ab.
22 "Pseudoautosomal homeobox-containing osteogenic gene".ti,ab.
23 or/1-22
24 human growth hormone/
25 (somatropin* or somatotropin* or somatotrophin* or genotropin* or saizen* or zomacton* or nutropin* or norditropin* or omnitrope* or humatrope*).ti,ab.
26 24 or 25
27 exp child/ or exp adolescent/ or exp infant/

28 child preschool/
29 (child* or infant* or adolescen* or girl* or boy* or prepubert* or pre-pubert*).ti,ab.
30 or/27-29
31 23 and 26 and 30
32 randomized controlled trial.pt.
33 controlled clinical trial.pt.
34 exp Randomized Controlled Trial/
35 exp Randomized Controlled Trials as Topic/
36 exp random allocation/
37 Double-Blind Method/
38 Single-Blind Method/
39 ((singl* or doubl* or trebl*) adj9 (blind* or mask*)).ti,ab.
40 placebo*.ti,ab,sh.
41 random*.ti,ab.
42 (medline or medlars or embase or scisearch or cinahl).ti,ab,sh.
43 (systematic* adj5 review*).mp.
44 (systematic adj5 overview*).mp.
45 (methodolog* adj5 review).mp.
46 (methodolog* adj5 overview).mp.
47 (methodolog* adj5 research*).mp.
48 meta analysis.pt.
49 meta-analysis.sh.
50 (meta-analys* or meta analys* or metaanalys*).mp.
51 ((hand adj5 search*) or (manual* adj5 search)).mp.
52 (electronic* database* or bibliographic* database* or computer* database* or online database*).mp.
53 (Health Technology Assessment* or Medical Technlogy Assessment*).ti,ab,in.
54 or/32-53
55 31 and 54
56 limit 55 to (english language and humans)
57 from 56 keep 1-331

Appendix 2 Data extraction forms

Data extraction form for primary studies

Reviewer:		**Date:**	**Version:**
Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Author et al., year (id) *Country* *Study design* *Number of centres* *Funding:*	(including, dose etc) 1. 2. *Duration of treatment:* *Other interventions used*:	*Target population:* *Number of Participants:* Total: 1. 2. *Sample attrition/dropout*: *Inclusion/exclusion criteria for study entry*:	*Primary outcomes:* *Secondary outcomes:* *Method of assessing outcomes:* *Length of follow-up:*

Characteristics of participants:			
	Treatment X (*specify)* (n=)	**Treatment Y (*specify)* (n=)**	**P Value**
Age, years			
Sex			
Results			
Outcomes	**Treatment X (*specify)* (n=)**	**Treatment Y (*specify)* (n=)**	**P Value**
Final height			
Comments			
Growth Velocity			
Comments			
Body composition			
Comments			
Other (specify)			
Comments			
QoL			
Comments			
Comments			
Adverse Effects			
Comments			
Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE			
Methodological comments • Allocation to treatment groups: • Blinding: • Comparability of treatment groups: • Method of data analysis: • Sample size/power calculation: • Attrition/drop-out:			

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

Quality criteria for assessment of observational studies

Cohort studies	
Is there sufficient description of the groups and the distribution of prognostic factors?	
Are the groups assembled at a similar point in their disease progression?	
Is the intervention/treatment reliably ascertained?	
Were the groups comparable on all important confounding factors?	

Was there adequate adjustment for the effects of these confounding variables?	
Was a dose-response relationship between intervention and outcome demonstrated?	
Was outcome assessment blind to exposure status?	
Was follow-up long enough for the outcomes to occur?	
What proportion of the cohort was followed-up?	
Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?	
Case-control studies	
Is the case definition explicit?	
Has the disease state of the cases been reliably assessed and validated?	
Were the controls randomly selected from the source of population of the cases?	
How comparable are the cases and controls with respect to potential confounding factors?	
Were interventions and other exposures assessed in the same way for cases and controls?	
How was the response rate defined?	
Were the non-response rates and reasons for non-response the same in both groups?	
Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?	
Was an appropriate statistical analysis used (matched or unmatched)?	
Case series	
Is the study based on a representative sample selected from a relevant population?	
Are the criteria for inclusion explicit?	
Did all individuals enter the survey at a similar point in their disease progression?	
Was follow-up long enough for important events to occur?	
Were outcomes assessed using objective criteria or was blinding used?	
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	

Data extraction form for Systematic Reviews

Reviewer:	**Date:**	**Version:**
Reference	**Methods**	
Study Ref: Author: Year: Country: Funding:	Aim/Objective: Search strategy: databases searched Inclusion criteria. *Interventions:* *Participants:* *Outcome measures:* *Study design:* Quality criteria: Application of methods: Methods for analysis	

Reviewer:	Date:	Version:
Reference	**Methods**	

Results

Quantity and quality of included studies

Treatment effect

Assessment of heterogeneity

Economic evaluation

Conclusions

Implications of the review

Methodological comments

- Search strategy
- Participants
- Inclusion/exclusion criteria
- Quality assessment of studies
- Method of synthesis

General comments

- Generalisability
- Funding

Quality Assessment for Systematic Reviews

1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	
2. Is there evidence of a substantial effort to search for all relevant research?	
3. Is the validity of included studies adequately assessed?	
4. Is sufficient detail of the individual studies presented?	
5. Are the primary studies summarised appropriately?	

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