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

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of growth hormone (GH) was evaluated in children suffering from growth hormone deficiency (GHD), Turner syndrome (TS), chronic renal failure (CRF), Prader-Willi syndrome (PWS) or idiopathic short stature (ISS). At the time of writing, the authors stated that GH was not currently licensed (in the UK) for use in ISS.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children (younger than 17 years) who were suffering from one of five conditions (GHD, TS, CRF, PWS or ISS).

Setting
The setting was secondary care. The economic study was carried out in Southampton, UK.

Dates to which data relate
The effectiveness data were derived from published studies dating from 1989 to 2000. The resource use data were derived from published and unpublished data in 1999 and 2001. The costs were presented at year 2000 prices.

Source of effectiveness data
The effectiveness data were derived from a systematic review of the literature.

Modelling
A separate model was developed for the cost-effectiveness analysis of the five conditions in the UK setting. A similar, deterministic decision tree approach was used. The same period of childhood growth was assessed, although the period varied under different scenarios.

Outcomes assessed in the review
The primary effectiveness outcomes assessed in the systematic review were:

the height (cm) at a given point in time, or at completion of growth (cm, standard deviation, or relative to adult norms);
the height standard deviation score (HtSDS);
the growth velocity (GV);
the GV relative to norms for same age children (GVSDS);
bone age;
body composition; and
psychological outcomes.

Quality of life measures were also eligible for inclusion, although none were found. Compliance rates and adverse events were not included in the analysis.

The primary epidemiological outcomes assessed by an ad hoc review of the literature were population data (i.e. weight, age, gender distribution), incidence, prevalence and current treatment patterns associated with each of the five conditions in children under the age of 17.

The parameters used in the model for the economic analysis included population data, the outcome measure, drop-out rate, average age at the start of treatment, average length of treatment, costs of treatment, drug doses and discount rate.

**Study designs and other criteria for inclusion in the review**

Randomised controlled trials (RCTs), or systematic reviews of RCTs, assessing the effects of GH in comparison with placebo or no intervention were eligible for inclusion. Where final height did not feature as an outcome in at least one of the trials for a particular condition, the authors considered other study designs (controlled studies, case-controlled studies, and case series) to assess this measure. Economic evaluations also formed part of the inclusion criteria, although none were found. The final cohort of included studies comprised a mixture of RCTs and non-RCTs.

**Sources searched to identify primary studies**

Published studies and statistics were consulted for epidemiological data and current treatment patterns. The Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, CRD databases (DARE, NHS EED and HTA), MEDLINE, PubMed, EMBASE, the National Research Register, the Science Citation Index, BIOSIS Previews, Econlit, the MRC Trials database, Early Warning System and Current Controlled Trials were searched for effectiveness data. All databases were searched from inception to April 2001 and were limited to articles reported in English. Further studies were identified by consultation with experts, and through bibliographies and industry submissions or trials (via NICE).

**Criteria used to ensure the validity of primary studies**

The validity of RCTs was assessed using the Jadad checklist. The validity of non-RCTs was judged using a modified version of the Spitzer criteria.

**Methods used to judge relevance and validity, and for extracting data**

One reviewer undertook the data extraction and validity assessment, with a second reviewer checking them. Any disagreements were resolved by discussion.

**Number of primary studies included**

Thirty-two studies were included in the review. There were 21 RCTs and 11 non-RCTs.

**Methods of combining primary studies**
The primary studies were combined in a narrative format and the results were structured according to the five health conditions. The authors stated that, owing to the heterogeneity amongst the studies, a meta-analysis was not possible. The range of results among the included studies was used for a sensitivity analysis of some of the parameters.

Investigation of differences between primary studies
Differences between the studies were discussed in a narrative.

Results of the review
Higher quality evidence existed for studies measuring short-term height outcomes (full details in report). However, model parameters were based upon final height gains. Base-cases were used in this analysis to reflect variations in measures of clinical effectiveness. Base-case 1 represented a larger effect size, while base-case 2 represented a more cautious estimate of effectiveness.

Effectiveness and epidemiological values used in the economic model are reported below (values for costs and discount rates are reported later). The data for final height assumed that the benefit was evenly spread over the treatment period.

GH in GHD.
In base-case 1, the length of treatment (assuming the child was aged 9) was 8 years and the final height gain was 10.28 cm. In base-case 2, the length of treatment was 5 years (assuming the child was aged 12) and the final height gain was 8.58 cm. The drug dose (based on average age- and sex-related weight at 50th percentile and not adjusted during puberty) was 0.175 mg/kg per week (range: 0.175 - 0.35). The assumed drop-out rate was 9.3% after the first year of treatment. Population data suggested 63% were boys.

GH in TS.
In base-cases 1 and 2, the length of treatment (assuming the child was aged 11) was 5 years. The final height gain was 4.8 cm in base-case 1 and 4.4 cm in base-case 2. The drug dose (based on average age- and sex-related weight at 50th percentile and not adjusted during puberty) was 0.30 mg/kg per week (range: 0.17 - 0.70). The assumed drop-out rate was 17% after the first year of treatment and 41% from monitoring after the first year of monitoring. Population data suggested that all were girls.

GH in CRF.
In base-case 1, the length of treatment (assuming the child was aged 14) was 3 years and the final height gain was 8.82 cm. In base-case 2, the length of treatment (assuming the child was aged 11) was 5 years and the final height gain was 3.48 cm. The drug dose (based on age- and sex-related weight at 50th percentile and not adjusted during puberty) was 0.33 mg/kg per week. The drop-out rate was 16% after the first year of treatment and 28% from monitoring after the first year of monitoring. Population data suggested that 68% were males.

GH in PWS.
In base-case 1, the length of treatment (assuming the child was aged 11) was 5 years (modeller's assumption). The height outcome was 1.4 HtSDS at 1 year and the drug dose was 0.233 mg/kg per week. In base-case 2, the length of treatment (assuming the child was aged 8) was 8 years. The final height gain was 10.38 cm (based on the distribution of final height in the general population) and the drug dose was 0.23 mg/kg per week. The drop-out rate was nil. The modellers assumed that 50% were males.

GH in ISS.
In base-case 1, the length of treatment (assuming the child was aged 10) was 6 years. The final height gain was 7.5 cm and the drug dose was 0.35 mg/kg per week (30 IU/m² per week; range: 0.35 - 0.70 mg/kg per week). In base-case 2,
the length of treatment (assuming the child was aged 9) was 7 years. The final height gain was 2.68 cm and the drug dose was 0.233 mg/kg per week (20 IU/m2 per week; range: 0.35 - 0.70 mg/kg per week). The drop-out rate was 29% after the first year of treatment and 30% from monitoring after the first year of monitoring. The modellers assumed that 60% were males.

Measure of benefits used in the economic analysis
The measure of benefits used for four of the five conditions (GHD, TS, CRF, ISS) was centimetres (cm) gained. In the analysis of PWS, the measure of benefit was cm or HtSDS at 1 year.

Direct costs
All direct costs relating to the health service perspective were included in the analysis. These were for drugs, outpatient and day admissions, district nurse, X-ray, magnetic resonance imaging and laboratory tests. The prices were taken from the British National Formulary (2001), the Personal Social Services Unit (University of Kent, 1999), and the Contracting Unit of Southampton University Hospitals Trust (2001). The resource quantities and the costs were reported separately. Discounting was conducted at 6.0% for costs and 1.5% for benefits (according to NICE guidelines).

Statistical analysis of costs
The data were deterministic.

Indirect Costs
In line with the chosen perspective, the indirect costs were not reported.

Currency
UK pounds sterling (£).

Sensitivity analysis
A range of parameter values was tested using one- and two-way sensitivity analyses. Such parameters included the length of treatment (range: 1 - 13 years), final height effect (range: 10 - 300% of the effect from the base-case from trials), GH dose (by indication), GH cost (range: 15 - 25/mg) and the annual range of discounting costs (range: 0 - 12%). The analysis was conducted according to the two chosen base-cases and then sub-divided into any of four scenarios that reflected important cost and practical factors that could influence successful treatment (full details were provided).

Estimated benefits used in the economic analysis
The incremental benefits were not reported separately (see 'Synthesis of Costs and Benefits' section).

Cost results
The authors provided a breakdown of costs (model inputs) reflecting UK practice conditions that were common to all five conditions. Full details were provided in the report. The discount rate for the costs was 6.0%. The results were reported for each of the five conditions according to specific event pathways derived from expert consensus. Additional model parameters were applied separately according to resource use for diagnosis and treatment (full details in report) as follows.

GH and GHD.

For base-case 1, the mean total cost of GH treatment was 55,712 and the mean incremental total cost per patient was
53,373. For base-case 2, these were 44,990 and 43,086, respectively. The mean costs of growth monitoring were 2,339 for base-case 1 and 1,904 for base-case 2.

GH and TS.

For base-cases 1 and 2, the mean total cost of GH treatment was 62,621 and the mean incremental total cost per patient was 61,770. The mean cost of growth monitoring was 852.

GH and CRF.

For base-case 1, the mean total cost of GH treatment was 54,617 and the mean incremental total cost per patient was 58,006. For base case 2, these were 69,390 and 68,425, respectively. The mean cost of growth monitoring was 611 in base-case 1 and 965 in base-case 2.

GH and PWS.

For base-case 1, the mean total cost of GH treatment was 56,663 and the mean incremental total cost per patient was 55,453. For base-case 2, these were 84,055 and 82,845, respectively, and for base-case 3, 70,882 and 69,263. The mean cost of growth monitoring was 1,210 for base-cases 1 and 2, and 1,620 for base-case 3.

GH and ISS.

For base-case 1, the mean total cost of GH treatment was 70,674 and the mean incremental total cost per patient was 69,234. For base-case 2, these were 51,023 and 49,488, respectively. The mean cost of growth monitoring was 1,440 in base-case 1 and 1,535 in base-case 2.

Synthesis of costs and benefits

The results were reported as incremental cost-effectiveness ratios according to the five conditions. All units were reported as the cost per cm gained, except for PWS which was the cost per HtSDS at 1 year.

GH and GHD.

The incremental cost/unit gained was 6.029 (range: 1.385 - 11.853) for base-case 1 and 5,708 (range: 1.660 - 11.209) for base-case 2.

GH and TS.

The incremental cost/unit gained was 15,997 (range: 4.690 - 36,855) for base-case 1 and 17,429 (range: 5.116 - 40,205) for base-case 2.

GH and CRF.

The incremental cost/unit gained was 7,403 (range: 2.468 - 15,530) for base-case 1 and 24,093 (range: 7.455 - 50,538) for base-case 2.

GH and PWS.

The incremental cost/unit gained was 40,815 (range: 10,873 - 121,341) for base-case 1, 85,368 (range: 17,760 - 169,877) for base-case 2, and 7,030 (range: 1.466 - 20,897) for base-case 3.

GH and ISS.

The incremental cost/unit gained was 13,498 (range: 4,295 - 134,978) for base-case 1 and 27,202 (range: 8,096 - 272,019) for base-case 2.

The sensitivity analysis results confirmed the sensitivity of the cost-effectiveness estimates. The most important factors
were the measure of effectiveness, GH dose, and costs associated with length of treatment.

Authors' conclusions
Growth hormone (GH) treatment can potentially increase short-term growth and improve final height, but it is an expensive alternative to growth monitoring. The utility of small gains in these areas will be dependent upon other factors, such as height in relation to peers and any psychological and health outcomes arising. More reliable evidence exists for short-term outcomes. Caution is required for final height results, owing to the limited number of very small, poorer quality studies measuring this outcome.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was provided for the study of the GH drug, it would appear to represent current practice for the treatment of the five conditions in the UK setting. You should decide if this represents current practice in your own setting. The authors chose placebo (or no intervention, defined as growth monitoring) as the comparator for the intervention drug. This allowed the active value of the treatment to be evaluated.

Validity of estimate of measure of effectiveness
A systematic review was undertaken to derive the clinical effectiveness parameters. The epidemiological parameters were taken selectively from the literature. The review was supported by an extensive database search, and some appropriate steps to minimise bias were employed. However, the lack of independent data extraction and validity assessment potentially limits the reliability of the findings. A narrative synthesis was adopted to derive estimates of effectiveness and, although this was supported by a discussion of study weighting according to methodological rigour, the quality of the studies was generally poor. There was a great deal of heterogeneity amongst the included studies and this was appropriately identified in the analysis of the results. To address these weaknesses in the effectiveness data, the authors undertook appropriate sensitivity analyses.

Validity of estimate of measure of benefit
The measures of benefit were cm and HtSDS gained. Final height was considered to be the more valid measure of effectiveness for the modelling, but very few good-quality studies were found to address this outcome.

Validity of estimate of costs
It appears that categories of costs relevant to the NHS and Personal Social Services were included in the analysis. The costs and the quantities were reported separately, thus enhancing the reproducibility of the study in other settings. The resource quantities and unit costs appear to have been reliably obtained from several published sources and from the authors' setting. A sensitivity analysis was appropriately conducted to reflect variations in GH dose, cost and annual discounting rate. The price year was reported, which will aid any future reflation exercise.

Other issues
The results are generalisable to the UK NHS. The authors stated that the results of this review require careful interpretation, given that the incorporated parameter values were not necessarily achievable in practice. The authors acknowledged other limitations of their study. These were related to the poor quality and heterogeneity of the included trials, and the inability to establish more robust evidence for final height outcomes. The authors made significant efforts to obtain quality of life data (utilities) from the literature and by considering a survey among TS sufferers and their parents. However, owing to various constraints, suitable data were not obtainable to formulate a cost-utility analysis. The authors noted that a cost-utility approach would be more informative to decision-makers since height gain is a condition-specific outcome and a link to health benefits from a gain in final height is not established.

Implications of the study
The authors suggested that, given that only a minority of children with a licensed condition are currently receiving GH
treatment in the UK, the budgetary impact of increased prescribing of GH treatment will require close examination. Specific recommendations are made for further large multi-centre RCTs focusing on final height and quality of life (provided as utilities) as outcome measures.

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None stated.

Bibliographic details

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