



Complete Summary

GUIDELINE TITLE

Human growth hormone (somatropin) in adults with growth hormone deficiency.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Human growth hormone (somatropin) in adults with growth hormone deficiency. London (UK): National Institute for Clinical Excellence (NICE); 2003 Aug. 34 p. (Technology appraisal; no. 64).

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Adult growth hormone deficiency

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To assess the clinical and cost effectiveness of recombinant human growth hormone (somatropin) in adults with growth hormone deficiency

TARGET POPULATION

Adults with growth hormone deficiency

INTERVENTIONS AND PRACTICES CONSIDERED

Recombinant human growth hormone (somatropin)

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
 - Quality of life
 - Mortality rate
- Cost effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the School of Health and Related Research (SchARR), University of Sheffield. (See the "Companion Documents" field.)

Identification of Studies

Search Methods

The aim of the search was to provide as comprehensive as retrieval as possible of studies relating to growth hormone deficiency and quality of life. The search strategy was designed to pick up quality of life studies relating to both treated and untreated populations.

Sources Searched

Nine bibliographic databases were searched providing coverage of the biomedical, psychology and health economic literature. A list of the databases is given in Table 1, Appendix 1 of the Assessment Report (see "Availability of Companion Documents" field). In addition the Southampton review was hand searched.

Keyword Strategies

Sensitive keyword strategies using freetext and, where available, thesaurus terms were developed. Strategies combined terms relating to growth hormone deficiency and quality of life. The quality of life component included general quality of life terms (e.g., quality of life, qol, hrqol), generic quality of life instruments (e.g., SF-36, EQ-5D, Nottingham Health Profile), and condition specific instruments (e.g., assessment of growth hormone deficiency in adults [AGHDA]). The list of quality of life instruments provided in the Southampton review was used to develop the keyword strategies. Keyword strategies for all databases are given in Appendix 1 of the Assessment Report (see "Availability of Companion Documents" field).

Search Restrictions

Date and language restrictions were not used. The search retrieval was not limited to specific study designs. Searches were undertaken in January 2002.

Inclusion and Exclusion Criteria

Controlled and uncontrolled trials and observational studies were included which reported quality of life, assessed over a period of time using quantitative measures, in adults aged 18 years or over with growth hormone deficiency who were either untreated or were treated with growth hormone in any dose.

Because many individuals with isolated idiopathic growth hormone deficiency (GHD) in childhood show normal growth hormone (GH) status when reassessed in adult life, studies were excluded which did not reassess at study entry the GH status of subjects with childhood-onset GHD.

Study Selection

Studies identified by the search strategy were assessed for inclusion as follows. Titles were initially considered for inclusion. If the titles suggested that the studies were relevant, the abstracts were then considered and, if these also appeared relevant, the full texts were then reviewed.

Relevant references from the retrieved articles were also included in the review.

NUMBER OF SOURCE DOCUMENTS

The electronic literature searches identified 1206 potentially relevant articles. A further 10 potentially relevant articles were identified from citations.

From their titles, 161 of these articles appeared potentially relevant; when their abstracts were read, this figure was reduced to 45; and 39 articles were retained when the full text had been reviewed. These 39 articles related to 34 relevant studies (see figure 1 of the Assessment Report [see "Availability of Companion Documents" field])--12 conventional randomised controlled trials (RCTs), five cross-over RCTs, eight prospective uncontrolled studies, four observational studies of treatment, one cohort study in untreated patients, and four miscellaneous studies.

Details of all these studies are provided in Appendix 2 of the Assessment Report (see "Availability of Companion Documents" field).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by the School of Health and Related Research (SchARR), University of Sheffield. (See the "Companion Documents" field.)

Quality Assessment

Randomised controlled trials (RCTs) were assessed for quality using the Jadad scale.

Data Synthesis

Meta-Analysis

The meta-analysis used the same assumptions and methods as the Southampton report. Full details are given in Appendix 1 of that report. The summary statistic generated was a weighted mean difference using a random effects model. Studies were weighted by the inverse of their variance.

The meta-analysis was constructed using STATA v 7.0 software (STATA Corp (2001) STATA Statistical Software: release 7.0, College Station, Tx: Stata Corporation).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

One economic evaluation and three cost studies were identified.

See Section 4.2 of the original guideline document for a detailed discussion of the cost-effectiveness analysis.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Recombinant human growth hormone (somatropin) treatment is recommended for the treatment of adults with growth hormone (GH) deficiency only if they fulfill all three of the following criteria.
 - They have severe GH deficiency, defined as a peak GH response of less than 9 mU/litre (3 ng/mL) during an insulin tolerance test or a cross-validated GH threshold in an equivalent test.
 - They have a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific "Quality of life assessment of growth hormone deficiency in adults" (QoL-AGHDA) questionnaire.
 - They are already receiving treatment for any other pituitary hormone deficiencies as required.
- The QoL status of people who are given GH treatment should be re-assessed 9 months after the initiation of therapy (an initial 3-month period of GH dose titration, followed by a 6-month therapeutic trial period). GH treatment should be discontinued for those people who demonstrate a QoL improvement of less than 7 points in QoL-AGHDA score.
- Patients who develop GH deficiency in early adulthood, after linear growth is completed but before the age of 25 years, should be given GH treatment until adult peak bone mass has been achieved, provided they satisfy the biochemical criteria for severe GH deficiency (defined as a peak GH response of less than 9 mU/litre [3 ng/mL] during an insulin tolerance test or a cross-validated GH threshold in an equivalent test). After adult peak bone mass has been achieved, the decision to continue GH treatment should be based on all the criteria (see above).
- Patients currently receiving GH treatment, for the management of adult onset GH deficiency, whether as routine therapy or as part of a clinical trial, could suffer loss of well being if their treatment were to be discontinued at a time they did not anticipate. Because of this, all National Health Service (NHS) patients who are on therapy at the date of publication of this guidance should have the option to continue treatment until they and their consultant consider it is appropriate to stop.
- Children with GH deficiency should be treated as outlined in the Institute's guidance on the use of GH in children (National Institute for Clinical Excellence [NICE] Technology Appraisal Guidance No. 42). At completion of linear growth (that is, growth rate
- Initiation of GH treatment, dose titration, and assessment of response during trial periods should be undertaken by a consultant endocrinologist with a special interest in the management of GH disorders. Thereafter, if maintenance treatment is to be prescribed in primary care, it is recommended that this should be under an agreed shared care protocol.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of recombinant human growth hormone (somatropin) in adults with growth hormone deficiency

POTENTIAL HARMS

Growth hormone (GH) side effects may include headache, arthralgia (joint pain), myalgia (muscle pain), fluid retention (peripheral oedema), mild hypertension, carpal tunnel syndrome, visual problems, nausea and vomiting, paraesthesia, antibody formation, and reactions at the injection site. Benign intracranial hypertension is a rare complication.

CONTRAINDICATIONS

CONTRAINDICATIONS

Growth hormone (GH) treatment is contraindicated in people with any evidence of tumour activity, in critically ill patients (for example, after complications following open heart or abdominal surgery, multiple trauma, acute respiratory failure or similar conditions) and also in patients with known hypersensitivity to GH or to any of the excipients. GH treatment is also contraindicated during pregnancy and lactation. In patients with tumours, anti-tumour therapy must be completed before starting GH therapy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation and Audit

- Clinicians who provide care for adults with growth hormone (GH) deficiency should review policies and practices regarding the prescription of GH in adults to take account of the guidance (see the "Major Recommendations" field).
- Local guidelines and care pathways on the treatment of adults with GH deficiency should incorporate the guidance.

- To measure compliance locally with the guidance, the following criteria can be used. Further details on suggestions for audit are presented in Appendix C of the original guideline document.
 - Recombinant human growth hormone (somatropin) treatment is given to an adult with GH deficiency only if he or she meets all of criteria a to c below or criterion d.
 - a. The individual has severe GH deficiency, defined as having a peak GH response of less than 9 mU/litre (3 ng/mL) during an insulin tolerance test (ITT) or a cross-validated GH threshold in an equivalent test.
 - b. The individual has a perceived impairment of quality of life (QoL), as demonstrated by a reported score of at least 11 in the disease-specific QoL-assessment of growth hormone deficiency in adults (QoL-AGHDA) questionnaire.
 - c. The individual is already receiving treatment for any other pituitary hormone deficiencies as required.
 - d. The individual is receiving GH treatment at the date of publication of this guidance and, following re-assessment by his or her consultant endocrinologist as part of routine follow-up, it is considered appropriate to continue the therapy, taking into account the guidance (see the "Major Recommendations" field).
 - An adult who is started on GH treatment is re-assessed for QoL status 9 months after the initiation of therapy. GH treatment is discontinued if the individual has a QoL improvement of less than 7 points in QoL-AGHDA score.
 - For an individual who as a child has been treated for GH deficiency and who has completed linear growth, the following are done.
 - GH treatment is stopped for 2-3 months.
 - The GH status of the individual is re-assessed.
 - GH treatment at an adult dose is re-started only if the individual has a peak GH response of less than 9 mU/litre (3 ng/mL) during an ITT, or a cross-validated GH threshold in an equivalent test.
 - If GH treatment is re-started, GH treatment at an adult dose is continued until adult peak bone mass is achieved.
 - When adult peak bone mass is achieved, GH treatment is continued only if the individual meets criteria a-c.
 - For an individual who develops GH deficiency in early adulthood, after linear growth is completed but before the age of 25, the following are done.
 - GH treatment should be given until adult peak bone mass is achieved if the individual has a peak GH response of less than 9 mU/litre (3 ng/mL) during an ITT, or a cross-validated GH threshold in an equivalent test.
 - When adult peak bone mass is achieved, GH treatment is continued only if the individual meets criteria a-c.
 - The following are carried out only by a consultant endocrinologist with a special interest in the management of GH disorders.
 - Initiation of GH treatment.
 - Dose titration.
 - Assessment of response during the trial period.
 - If maintenance GH treatment is to be prescribed in primary care, there is an agreed shared-care protocol.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Foreign Language Translations
Patient Resources
Quick Reference Guides/Physician Guides
Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Clinical Excellence (NICE). Human growth hormone (somatropin) in adults with growth hormone deficiency. London (UK): National Institute for Clinical Excellence (NICE); 2003 Aug. 34 p. (Technology appraisal; no. 64).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Aug

GUIDELINE DEVELOPER(S)

National Institute for Health and Clinical Excellence (NICE) - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Committee Members: Dr Tom Aslan, General Practitioner, Stockwell, London; Professor David Barnett (*Chair*) Professor of Clinical Pharmacology, University of Leicester; Professor Sir Colin Berry (term of office ended October 2002) Retired Professor of Morbid Anatomy & Histopathology, The Royal London Hospital; Dr Sheila Bird, MRC Biostatistics Unit, Cambridge; Professor Rosamund Bryar, Professor of Community & Primary Care Nursing, St Bartholomew's School of Nursing & Midwifery, London; Dr Karl Claxton, Health Economist, University of York; Dr Richard Cookson, Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich; Professor Sarah Cowley (term of office ended October 2002) Professor of Community Practice Development, Kings College, London; Professor Nicky Cullum (up to January 2002) Professor in Health Sciences/Director, Centre for Evidence-based Nursing, University of York; Mr Chris Evennett (up to June 2002) Chief Executive, Mid-Hampshire Primary Care Trust, Winchester; Professor Terry Feest, Clinical Director & Consultant Nephrologist, Richard Bright Renal Unit, & Chair of UK Renal Registry, Bristol; Professor Gary A Ford, Professor of Pharmacology of Old Age/Consultant Physician, Newcastle upon Tyne Hospitals NHS Trust; Ms Jean Gaffin (up to February 2002) Formerly Executive Director National Council for Hospice and Specialist Palliative Care Service; Mrs Sue Gallagher (term of office ended October 2002) Former Chief Executive, Merton, Sutton & Wandsworth Health Authority, London; Ms Bethan George, Interface Liaison Pharmacist, Tower Hamlets PCT and Royal London Hospital, Whitechapel; Dr Trevor Gibbs, Head, Global Clinical Safety & Pharmacovigilance, GlaxoSmithKline, Greenford; Mr John Goulston, Director of Finance, St Bartholomew's Hospital & the London NHS Trust; Dr Terry John, General Practitioner, The Firs, London; Dr Diane Ketley (term of office ended August 2002) Research into Practice Programme Leader, NHS Modernisation Agency, Leicester; Dr Mayur Lakhani (term of office ended August 2002) General Practitioner, Highgate Surgery, Leicester, & Lecturer, University of Leicester; Mr Muntzer Mughal, Consultant Surgeon, Lancashire Teaching Hospitals NHS Trust, Chorley; Mr James Partridge, Lay Representative; Chief Executive, Changing Faces, London; Mrs Kathryn Roberts, Nurse Practitioner, Hyde, Cheshire; Professor Philip Routledge, Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff; Ms Anne Smith, Consultant (Management) and Trustee of the Long-Term Medical Conditions Alliance; Professor Andrew Stevens (*Vice-Chair*) Professor of Public Health, University of Birmingham; Dr Cathryn Thomas, General Practitioner, & Senior Lecturer, Department of Primary Care & General Practice, University of Birmingham; Dr Norman Vetter, Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff; Dr David Winfield, Consultant Haematologist, Royal Hallamshire Hospital, Sheffield

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Human growth hormone (somatropin) in adults with growth hormone deficiency. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Aug. 2 p. (Technology appraisal 64). Available in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).
- Clinical and cost effectiveness of recombinant human growth hormone (Somatropin) in adults: report by a Consortium from the School of Health and Related Research (ScHARR), University of Sheffield. 2002 Apr 10. 147 p. Available in Portable Document Format (PDF) from the [NICE Web site](#).
- QoL-AGHDA: Quality of life—assessment of GH deficiency in adults. Pharmacia AB. 2003 Aug 27. 4 p. Available in Portable Document Format (PDF) from the [NICE Web site](#).

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N0266. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria can be found in Appendix C of the [original guideline document](#)

PATIENT RESOURCES

The following is available:

- The use of human growth hormone (somatropin) for adults with growth hormone deficiency. Understanding NICE guidance – information for people with growth hormone deficiency, and the public. London (UK): National Institute for Health and Clinical Excellence (NICE); 2003 Aug. 10 p. (Technology appraisal 64).

Electronic copies: Available in English and Welsh in Portable Document Format (PDF) from the [National Institute for Health and Clinical Excellence \(NICE\) Web site](#).

Print copies: Available from the Department of Health Publications Order Line 0870 1555 455. ref: N0268. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By

providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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