NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Human Growth Hormone in Children (Review)

Comments received from consultees and commentators on the draft scopes issued for consultation

This document contains two tables of comments.

A draft scope was issued to consultees and commentators in October 2007. Comments received on this scope are shown in the first table

A second draft was issued to consultees and commentators in April 2008. The second table shows these comments.

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Health Technology Appraisal
Human Growth Hormone in Children (Review)

Comments received from consultees and commentators on the draft scope issued for consultation in October 2007

Section	Consultees	Comments	Action
Background information	Cochrane Metabolic and Endocrine Disorders Group	satisfying; comment (last para): since idiopathic short stature is not a disease these children should not be called 'patients'	Scope amended. See paragraph 6 on page 2 of the scope.
	Department of Health	The second paragraph of the background refers to 'short gestational age': Could you please consider amending this to read 'small for gestational age'.	Scope amended
	Turner Syndrome Support Society [UK] [TSSS]	As regards TS, reasonably accurate	Comment noted
	Welsh Kidney Patients Association	No Comment	Comment noted
	Ipsen Limited	Agree with the background information provided for the treatment of growth hormone in children and no further comments to add to this section. Ipsen also have the following indication approved in adults: Replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult –onset aetiology	Comment noted Comment noted. Human growth hormone as a treatment for growth failure in adults is outside the remit of this appraisal.

Section	Consultees	Comments	Action
	Eli Lilly	Please note that the SGA indication is more accurately termed 'short children born small for gestational age (SGA)'.	Scope amended. See paragraph 2 on page 1 of the scope.
		Turner syndrome is the 'complete or partial' lack of one X chromosome.	Scope amended. See paragraph 4 on page 1 of the scope.
		It would be helpful if the untreated final height data (and other data) presented were substantiated by citing the reference sources.	Scopes are normally brief documents and references are not cited.
	Merck Serono	We would suggest the title for this appraisal may be amended to be made more specific for the specified paediatric population and include a mention of age or bone age to be considered.	The title of the appraisals is derived from the remit referred to the Institute by the Department of Health and cannot be changed.
		In the second paragraph of the background section it is noted that growth failure is a prominent feature for a series of groups of patients. In particular, "in children short for gestational age (SGA)", we would suggest that this wording be made more specific to, "in short children born small for gestational age", to be more specific	Scope amended. See paragraph 2 on page 1 of the scope.
	Novo Nordisk Ltd	SGA is an abbreviation for 'small for gestational age'. Furthermore, children are not born with SGA, but are born SGA.	Scope amended. See paragraph 2 on page 1 of the scope.
		Turner Syndrome is caused by a missing or incomplete X chromosome.	Scope amended. See paragraph 4 on page 1 of the scope.
		Please include references, particularly for the incidence and untreated final height figures.	Scopes are normally brief documents and references are not cited.
	Sandoz Ltd	We consider the background information to be accurate and complete	Comment noted.

Section	Consultees	Comments	Action
	Pfizer UK Ltd	Page 1 Paragraph 1 The list of physiological effects of GH is missing effects on water and mineral metabolism.	Scope amended. See paragraph 1 on page 1 of the scope.
		A more specific description of tissue growth is required to include stimulation of skeletal muscle growth. We suggest inclusion of the following sentence from the current genotropin SPC to reflect influence of GH on overall body composition: "GH maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat."	Scopes are normally brief documents and references are not cited.
		Paragraph 3 According to the guidelines on the BSPED website (http://www.bsped.org.uk/professional/guidelines/index.htm) the final height for males suffering from GHD is 134-146 cm. For females it is 128-134cm.	Scope amended. See paragraph 3 on page 1 of the scope.
		Paragraph 4: The mean final height in TS is 147 cm.	Comment noted. The mean final height in TS was taken from the assessment report that informed the original appraisal (Technology Appraisal Guidance 42).

Section	Consultees	Comments	Action
		Page 2: Paragraph 2: PWS: We would like to challenge the last sentence. There are many data indicating reduced GH secretion in patients with Prader-Willi syndrome. Low peak GH response to stimulation tests, decreased spontaneous GH secretion, and low serum IGF-I levels have been documented in at least 15 studies involving about 300 affected children. Depending on the stimulation test used, 40-100% of children with this condition fulfil the criteria for GH deficiency, which is generally defined as peak GH levels of less than 10mU/litre in response to one or two stimulation tests.(Burman P. Endocrine Reviews 22 (6):787-799). Paragraph 4 : Statement on SGA is very brief and not really informative	The sentence has been deleted. Scopes are normally brief documents and references are not cited.
The technology/ intervention	Cochrane Metabolic and Endocrine Disorders Group	yes	Comment noted.
	Department of Health	We agree with this description	Comment noted.
	Turner Syndrome Support Society [UK] [TSSS]	Yes	Comment noted.
	Welsh Kidney Patients Association	No Comments	Comment noted.
	Ipsen Limited	Same as the above. Agree with the indication stated for children and for adults as stated above.	Comment noted.
	Merck Serono	Yes	Comment noted.

Section	Consultees	Comments	Action
	Novo Nordisk Ltd	The product manufactured by Novo Nordisk is called Norditropin SimpleXx	Scope amended. See table on page 3 of the scope.
	Sandoz Ltd	Yes the description of the technology is accurate	Comment noted.
	Pfizer UK Ltd	Somatropin (Genotropin ®) is administered as a sub-cutaneous injection and the dose may vary according to the indication being treated.	Comment noted.
Licensing issues (only for manufacturers to complete)	Ipsen Limited	No other information available in the public domain	Comment noted.
	Eli Lilly	Humatrope (Lilly) has a licence for SGA Commercial in confidence information removed	Comment noted.
	Merck Serono	No further Licenses are currently pending.	Comment noted.
	Novo Nordisk Ltd	Commercial in confidence information removed	Comment noted.
	Sandoz Ltd	Sandoz have no licences pending at this time	Comment noted.
	Pfizer UK Ltd	Commercial in confidence information removed	Comment noted.
Population	Cochrane Metabolic and Endocrine Disorders Group	yes; (see comment “Other considerations)	The definition of the population was discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Department of Health	We are happy with this definition – we feel that a group for separate consideration is children with growth disturbance, as per licensed indication for each preparation available	The definition of the population was discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Turner Syndrome Support Society [UK] [TSSS]	Is the population defined appropriately? Yes Are there groups within this population that should be considered separately? No	The definition of the population was discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Welsh Kidney Patients Association	The WKPA only has knowledge of growth problems with children with renal failure, so can not comment on the other groups mentioned in the information.	Comment noted.
	Southampton Health Technology Assessments Centre	Can NICE clarify whether children are defined as being under 16 or 18 years old? The proposed population is heterogeneous and would be difficult to include in a single review. 1) SHOX deficiency is linked with short stature in a variety of syndromes, but is not in itself a disease. There are also implications for genetic testing – how routinely is this done? Inclusion of people with this deficiency as a specific group therefore seems inappropriate.	The definition of the population was discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
		2) As stated in the scope, children can be born small for gestational age (SGA) for a variety of reasons, and this is not linked to any specific disease. This condition is also referred to as low birth weight, or intrauterine growth restriction. There are several definitions of SGA, e.g. having a weight below the 10^{th} percentile for GA, but the scope suggests the group would be limited to children born SGA with a current height of SDS -2.5 and parental adjusted height of SDS-1.The BNF indicates growth disturbance in short children born small for gestational age whose growth has not caught up by 4 years or later. There are therefore different definitions of SGA, and conditions can include other metabolic abnormalities. Most importantly, SGA does not distinguish between those who are just small, and those who have a growth restriction relative to their peers. It is therefore hard to define a specific SGA patient group for inclusion in the review, and we think the scope needs more justification and clarification for this diverse patient group.	Scope amended. See page 3 of scope. The definition of the population was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
		3) Commercial in confidence information removed. The scope states that 'idiopathic short stature is not a disease and therefore specific diagnostic criteria cannot be used to determine who has ISS." It therefore does not seem appropriate to include it in the current appraisal.	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
	Ipsen Limited	In children – population is defined appropriately. In adults – population is not included	Comment noted.
	Eli Lilly	We suggest that Idiopathic short stature (ISS) is not included in this appraisal due to the inherent uncertainty in the regulatory process and potential impact on appraisal timelines	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
	Merck Serono	We believe this is defined appropriately	Comment noted.
	Sandoz Ltd	The population is adequately defined, we see no clinical reason why they should be discussed separately	Comment noted.
	Pfizer UK Ltd	We require clarification as to whether the ISS indication will be included in this appraisal. It is not clear from the information given in paragraph 5, page 2.	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
Comparators	Cochrane Metabolic and Endocrine Disorders Group	yes	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Department of Health	Yes – we are happy with this treatment	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Welsh Kidney Patients Association	No comment	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Southampton Health Technology Assessments Centre	The scope lists 'management strategies without somatropin'. Does this include growth monitoring?	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Ipsen Limited	Yes	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Eli Lilly	There are no standard treatments which could be used as comparators	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Merck Serono	We believe this is defined appropriately	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Novo Nordisk Ltd	There are no standard treatments to compare with human growth hormone.	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Sandoz Ltd	Yes these are the standard treatments used within the NHS	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Pfizer UK Ltd	There are no standard treatments available in the NHS to which the technology should be compared.	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
Outcomes	Cochrane Metabolic and Endocrine Disorders Group	yes; comment: investigators should be careful with the outcome “near final height” (in case this would be eventually used)	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Department of Health	We feel that this seems likely, if these capture timing of optimal intervention.	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Turner Syndrome Support Society [UK] [TSSS]	Yes	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Welsh Kidney Patients Association	No comment	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

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	Southampton Health Technology Assessments Centre	These seem to be appropriate measures. However, not all of these outcomes may be available for all of the conditions to be considered in this review. This will be particularly important if the MTA limits the inclusion criteria to RCTs, which do not often report the ideal measure of Final Height.	The Institute recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. See the technology appraisals methods guide: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
	Ipsen Limited	Yes	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Eli Lilly	There are difficulties in measuring quality of life in paediatric indications for GH. Therefore, it will be important to reflect the impact of childhood treatment on adult quality of life i.e. the relationship between adult height and quality of life.	The limited health related quality of life data available was acknowledged at the scoping workshop in June 2008. However, it was agreed at the scoping workshop that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
	Merck Serono	We believe this is defined appropriately	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Novo Nordisk Ltd	Please include bone mineral density and lipid profile as outcome measures	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Sandoz Ltd	Yes, the outcomes cover quality of life, safety and efficacy of the product	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
	Pfizer UK Ltd	The outcomes listed will capture the most important health benefits, however we would suggest the following additional outcomes capturing potential beneficial effects on metabolism, which is more relevant with transitional treatment and SGA: - glucose tolerance / insulin sensitivity - effects on lipid profile – LDL / HDL cholesterol, triglycerides - bone mineral density / bone mineral content <u>Cognitive function</u> We would challenge the inclusion of Cognitive function as an accepted outcomes measure for GH treatment. Research conducted in 2003 concluded that there was no significant differences in cognition or behaviour in PWS (Haqq AM, Stadler DD, Jackson RH, Rosenfeld RG, Purnell JQ, LaFranchi SH. Effects of growth hormone on pulmonary function, sleep quality, behavior, cognition, growth velocity, body composition, and resting energy expenditure in Prader-Willi syndrome. J Clin Endocrinol Metab. 2003 May;88(5):2206-12)	The outcomes were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

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		Quality of life (QoL) The measurement of quality of life in children is associated with a number of issues (for example, lack of adequate methods, different ages of children investigated, different areas of QoL in different ages) and therefore there is a paucity of data in this area. The lack of QoL data may present certain challenges when undertaking the economic modelling.	The limited health related quality of life data available was acknowledged at the scoping workshop in June 2008. However, it was agreed at the scoping workshop that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
Economic analysis	Cochrane Metabolic and Endocrine Disorders Group	The time horizon should be specified in more detail (for example up to 14 years in Turner Syndrome.	The time horizon of the economic analysis is not defined in the scope but will be considered as part of the appraisal.
	Department of Health	We feel that the optimal starting time of treatment/replacement needs clarification, and a need for guidance on transition to adult care.	The scope has been amended to include consideration the transition of care from paediatric to adult endocrine services of young people whose linear growth is not complete. See 'Other considerations' in the table on page 5 of the final scope. This has been discussed following consultation. It was agreed that the evaluation of the optimal starting time of treatment was outside the remit of this appraisal.

Section	Consultees	Comments	Action
	Turner Syndrome Support Society [UK] [TSSS]	The time horizon for the benefit of added height is the life time of the individual	The time horizon of the economic analysis is not defined in the scope but will be considered as part of the appraisal.
	Welsh Kidney Patients Association	No comment	Comment noted.
	Southampton Health Technology Assessments Centre	The original economic model for the original review used cost/cm gained as an output. It would be difficult to translate this into cost/QALY, unless more QoL data has become available since the last review. An additional consideration will be consistency of outcomes across groups. There may be QoL data for some conditions but none for others, in which case cost/QALY cannot be calculated fairly for all patient groups/conditions. If life expectancy is different for the identified conditions, this would require separate models for calculation of cost/QALY. This would have an impact on the workload, and it may not be feasible to calculate this (even where QoL data exist) for all the specified conditions within the resources for this project. As SGA and ISS would be hard to define, it might be difficult to populate an economic model with suitable data. Also, it might not be sensible to aggregate all the possible causes for these conditions onto the same model if key patient characteristics differ.	The limited health related quality of life data available was acknowledged at the scoping workshop in June 2008. However, it was agreed at the scoping workshop that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
	Ipsen Limited	No further comments	Comment noted.
	Eli Lilly	The time horizon has to be sufficiently long to incorporate the increase in height in adults and the associated impact on quality of life	The time horizon of the economic analysis is not defined in the scope but will be considered as part of the appraisal.
	Merck Serono	We believe this is defined appropriately	Comment noted.
	Sandoz Ltd	We have no further comments on the economic analysis	Comment noted.

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	Pfizer UK Ltd	We appreciate that a cost per QALY output is generally required by NICE when Technology Appraisals are undertaken. However, it is widely acknowledged that quality of life data is not routinely measured in HGH trials involving children. Therefore a pragmatic approach to modelling, including the need to look for alternative data sources to support the model, will need to be considered.	The limited health related quality of life data available was acknowledged at the scoping workshop in June 2008. However, it was agreed that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
Other considerations	Cochrane Metabolic and Endocrine Disorders Group	▪ I would suggest change the title to "Human growth hormone in children and adolescents" unless the appropriate age boundaries are included in the definition of "children". ▪ Children with growth disturbances associated with being born small for gestational age and children with idiopathic short stature might be mixed or could actually - at least in part -represent the same study population. Investigators will therefore have to critically appraise diagnostic accuracy in the included studies.	The title of the appraisal was derived from the remit that was issued by the Department of Health. The remit did not refer to 'adolescents' but 'children'. Comment noted. The scope states "*Costs for any diagnostic tests related to the treatment decision should be included in the economic analysis"* in the section headed 'Any other considerations'.
	Department of Health	In our view, the scope of the appraisal should by focused on the licensed use of growth hormone in treating growth deficiencies, and other growth failure in children (caused by underlying clinical conditions).	Comment noted.
	Welsh Kidney Patients Association	It is very important that parents/and or guardians and children when old enough are of possible side effects of the drug	Adverse events associated with the technologies will be included in the appraisal.
	Ipsen Limited	No further comments	Comment noted.

Section	Consultees	Comments	Action

	Merck Serono	• We believe it is most appropriate to keep the assessment of somatropin as one appraisal rather than splitting it out into separate appraisals for two primary reasons:
		  • Firstly, one piece of guidance in this area will aid accessibility and implementation of this guidance;
		  • Secondly, patient groups identified for the separate indicated populations may be very small and as a result may not warrant separate assessment.
		
		• We believe the standard comparator for somatropin would be providing no treatment.
			Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
			
			The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Merck Serono	• With regards the transition from paediatric to adult use of growth hormone, the literature would suggest that continuation of growth hormone once final height has been attained, is beneficial for tissue maturation; bone mass, muscle mass and strength mature several years after longitudinal skeletal growth has ceased [1]. Optimum dosing strategies have yet to be defined, however we would consider that other consultees in this process would be better informed, than ourselves, to provide opinion on this subject. • With regards the evidence available to define the optimal starting age and length of growth hormone treatment for girls with TS, the literature would suggest that, the earlier treatment commences and the longer the duration of treatment, before final height is reached, the more favourable the outcome [2,3]. Commencing treatment prior to the age of eight has been suggested by BSPED [4]; we would consider that other consultees in this process, such as BSPED, would be better informed than ourselves, to provide opinion on this subject. References 1. Shalet S, Horm Res 2004; 62(suppl 4):15-22. Stepping into Adulthood: The Transition Period 2. Carel J-C, JCEM 2005; 90(6):3793–3794. Editorial: Growth Hormone in Turner Syndrome: Twenty Years after, What Can We Tell our Patients? 3. Betts PR, Butler GE, Donaldson MDC, Dunger DB, Johnston DI, Kelnar CJH, Kirk J, Price DA, Wilton P, the UK KIGS Executive Group on behalf of the participating centres. A decade of growth hormone treatment in girls with Turner syndrome in the UK. *Arch Dis Child* 1999; 80: 221-25 4. http://www.bsped.org.uk/professional/position/docs/turner.htm	This has been discussed following consultation. It was agreed that the evaluation of the optimal dosing strategies was outside the remit of this appraisal. This has been discussed following consultation. It was agreed that the evaluation of the optimal starting age for treatment was outside the remit of this appraisal.
	Sandoz Ltd	We feel that the appraisal should also cover the different formulations available and also level of home care service available to patients	The different products will be appraised according to their market authorisation. The evaluation of home care services available to patients is outside the remit of the appraisal.

Section	Consultees	Comments	Action
	Pfizer UK Ltd	We would recommend that this re-review considers the contribution that an Observational Database can make to this re-review (for example, treatment outcomes and safety data on substantial numbers of patients). We would also recommend that the Value Added Services which Manufacturers can offer (for example, the dedicated support service that can be offered to help healthcare professionals, patients and their carers to manage their treatment) are considered.	The Institute recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. See the technology appraisals methods guide: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
Any additional comments on the draft scope	Cochrane Metabolic and Endocrine Disorders Group	The topic should probably not be split into more than one appraisal since although there are a number of indications for somatropin the number of appropriate studies (randomised and controlled clinical trials) is limited	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
	Department of Health	The Department of Health has no additional comments to offer	Comment noted.

Section	Consultees	Comments	Action
	Turner Syndrome Support Society [UK] [TSSS]	Questions for consultation -Question 4. The evidence available to define the optimal starting age. The usual generalisation regarding GH treatment for height improvement is that the younger the subject the better the response, both in the short term (1st years of treatment) and in the long term (to adult height). Age was one of the predictors of growth response over the 1st 4 years of GH treatment in TS [reference 1] in a mathematical model based on a retrospective study and validated in a separate population of TS girls; the younger, the better the response over 4 years. Also in a study of more than a 1000 TS girls reaching (near) adult height [reference 2], the gain in height was negatively correlated to the age at start of GH. A recently published study (a randomised, controlled, open-label, multi-centre trial) [reference 3] of 88 TS girls treated before 4 years of age showed that GH treatment prevented the loss in height that occurs in the early years of TS over a 2 year period. They concluded that “Early GH treatment can correct growth failure and normalise height in infants and toddlers with TS”. In discussion they remark that early normalisation of height has a number of potential benefits for young girls with TS, including prevention of stature-related juvenilisation and mascotism, improvement of peer-group integration, reduction of the gap between the subject’s height and the target height (height expected within the family), and the opportunity to induce puberty with oestrogen at a physiologically appropriate age. References 1] Ranke MB et al 2000 J Clin Endocrinol Metab 85 4212-8 2] Ranke MB and Lindberg A 2007 “Growth Hormone Therapy in Pediatrics – 20 Years of KIGS” Basel, Karger pp 332-339 3] Davenport ML et al 2007 J Clin Endocrinol Metab 92 406-3416	This has been discussed following consultation. It was agreed that the evaluation of the optimal starting age for treatment was outside the remit of this appraisal.

Section	Consultees	Comments	Action
	Turner Syndrome Support Society [UK] [TSSS]	an important reference as well as the British National Formulary for Children (2005)plus the English Adult Renal NSF addresses issues with prescribing in renal disease. The Welsh Renal NSF for Children states that “children with CKD or ERF are often on multiple therapies which may be altered frequently depending on laboratory and other tests. Although they may have interaction with primary, secondary and tertiary care and knowledge of current medication is often unavailable. Patient recall of drugs may be variable and an up-to-date written or electronic patient record would be helpful, and could provide an accurate record available to prescribers and additional reassurance for patients. As part of the education for the child and carer, an understanding of the reasons for each drug prescribed and its associated side-effects must be given” The renal children’s unit at the university hospital of Wales Cardiff is part of the renal associations programme ”renal patients view” where all patients can view their results on a secure web site. the WKPA supports the view of an electronic records for patients	
	Welsh Kidney Patients Association	Children’s standard 7 of the Welsh Renal Service Framework deals with medicines for children and young people with CKD and ESRF. The rationale behind the standard states that standard 10 of the English NSF for children is	Comment noted.

Section	Consultees	Comments	Action
	Southampton Health Technology Assessments Centre	Questions for consultation: 1. Yes, we think the topic should be split into more than one appraisal. In particular, SHOX and SGA could be considered separately since a) they are not specific diseases and b) they will require a new review rather than an update of an existing review (as for GHD, CRI, TS, ISS and PWS). 2. Standard comparator could be defined as growth monitoring. 3. the evidence available to define the optimal dosing strategies in the management of patients in transition from paediatric to adult care. Will be dependent on what data is found in the included studies. 4. the evidence available to define the optimal starting age and length of GH treatment for girls with TS. Will be dependent on what data is found in the included studies. 5. the evidence available to define the optimal treatment strategies of GH treatment for children with PWS. Will be dependent on what data is found in the included studies.	1. Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature. 2. The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop. 3. This has been discussed following consultation. It was agreed that the evaluation of the optimal dosing strategies was outside the remit of this appraisal. 4. This has been discussed following consultation. It was agreed that the evaluation of the optimal starting age for treatment was outside the remit of this appraisal. 5. This has been discussed following consultation. It was agreed that the evaluation of the optimal treatment strategies was outside the remit of this appraisal.

Section	Consultees	Comments	Action
	Eli Lilly	Responses to consultation questions • whether this topic should be split into more than one appraisal because of the large number of indications for somatropin. If yes, how should the indications be grouped? We think it is ok to appraise together in one appraisal	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
		• how standard comparators should be defined. We don't think that there are any realistic comparators	The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.
		• the evidence available to define the optimal dosing strategies in the management of patients in transition from paediatric to adult care. P E Clayton, R C Cuneo, A Juul, et al. Consensus statement on the management of the GH-treated adolescent in the transition to adult care European Journal of Endocrinology 2005; 152: 165–170	This has been discussed following consultation. It was agreed that the evaluation of the optimal dosing strategies was outside the remit of this appraisal.

Section	Consultees	Comments	Action
	Eli Lilly	P. E. Clayton, S. Cianfarani, P. Czernichow, et al. CONSENSUS STATEMENT: Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society J Clin Endocrinol Metab 2007; 92: 804–810 Shalet et al. Effect of growth hormone (GH) treatment on bone in postpubertal GH-deficient patients: A 2-year randomized, controlled, dose-ranging study. J. Clin. Endocrinol. Metab. 2003; 88: 4124-4129. Attanasio et al. Continued growth hormone (GH) treatment after final height is necessary to complete somatic development in childhood-onset GH-deficient patients. J. Clin. Endocrinol. Metab.2004; 89: 4857-4862.	
		• the evidence available to define the optimal starting age and length of GH treatment for girls with TS. There has been a recent Lilly publication: Davenport et al. Growth hormone treatment of early growth failure in toddlers with Turner syndrome: A randomised, controlled, multicenter trial. J Clin Endocrinol Metab 2007; 92: 3406-3416.	This has been discussed following consultation. It was agreed that the evaluation of the optimal starting age for treatment was outside the remit of this appraisal.
		• the evidence available to define the optimal treatment strategies of GH treatment for children with PWS. We are not licensed for this indication	This has been discussed following consultation. It was agreed that the evaluation of the optimal treatment strategy was outside the remit of this appraisal. .

Section	Consultees	Comments	Action
	Novo Nordisk Ltd	We are happy for all the indications to be appraised together	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature.
	Pfizer UK Ltd	Questions for consultation included in Draft Scope: • whether this topic should be split into more than one appraisal because of the large number of indications for somatropin. If yes, how should the indications be grouped? Pfizer do not recommend that the scope should be split into more than one appraisal. • how standard comparators should be defined. We are not aware of any standard comparators.	Following discussion with the Department of Health, the scope for this appraisal was split. The remit for this appraisal no longer includes idiopathic short stature. The comparators were discussed at the scoping workshop in June 2008. The final scope reflects what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
		• the evidence available to define the optimal dosing strategies in the management of patients in transition from paediatric to adult care. Pfizer would like to suggest that the Committee consider this question in terms of a Clinical Guideline rather than a Technology appraisal, since the question is concerned with patient management in terms of dosing strategies. However, we can support the response to the question with the following publication, using data from the KIGS database: Hoybye C, Jonsson P, Monson J, Koltowska-Haggstron M, Hana V, Geffner M, Abs R. "Impact of the primary aetiology upon the clinical outcome of adults with childhood-onset GH deficiency" Eur J Endocrinology 2007 157 1-9 The answer to the above question can be supported by Chapter 12 in the recently published book 'Growth Hormone Therapy in Pediatrics 20 Years of KIGS. Karger ISBN 978-3-8055-8256-8 '"Effect of Prior Pediatric Growth Hormone Replacement on Serum Lipids and Quality of Life in Young Adults with Reconfirmed Severe Growth Hormone Deficiency: The Combined KIGS and KIMS Experiences" Geffner M, Jonsson P, Monson J, Abs R, Hana V, Hoyboy C, Koltowska-Haggstrom M. • the evidence available to define the optimal starting age and length of GH treatment for girls with TS. The following publications, using data from the KIGS database, supports the response to the above question:	This has been discussed following consultation. It was agreed that the evaluation of the optimal dosing strategies was outside the remit of this appraisal. This has been discussed following consultation. It was agreed that the evaluation of the optimal starting age for treatment was outside the remit of this appraisal.

Section	Consultees	Comments	Action
		Ranke M, Lindberg A, Ferrandez-Longas, A, Darendeliler F, Albertsson-Wikland K , Dunger, D, Chatelain P, , Cutfield W, Tauber M, Wilton P, Wollman H, Reiter E. On behalf of the KIGS International Board. “Major determinants of Height and Development in Turner Syndrome (TS). Patients treated with GH: Analysis of 987 patients from KIGS.” Paediatric Research Vol 61 No 1 2007 pages 105-110. Ranke M, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price D. On behalf of the KIGS International Board. “Prediction of Long Term Response to Recombinant Human Growth Hormone in Turner Syndrome: Development and Validation of Mathematical Models” Journal of Clinical Endocrinology and Metabolism Vol 85 No 11 2000 pages 4121-4218 • the evidence available to define the optimal treatment strategies of GH treatment for children with PWS. We cannot assist with answering this question at this stage.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

NHS Quality Improvement Scotland

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal
Human Growth Hormone in Children (Review)

Comments received from consultees and commentators on the draft scope issued for consultation in April 2008

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Ipsen Limited	Agree with the information provided for the treatment of growth hormone in children and no further comments to add to this section. Ipsen also have the following indication approved in adults: Replacement of endogenous growth hormone in adults with growth hormone deficiency of either childhood or adult –onset etilogy.	Comment noted. Human growth hormone as a treatment for growth failure in adults is outside the remit of this appraisal. No action required.
	Pfizer Limited	Page 1, Paragraph 1 The list of physiological effects of GH is missing effects on water and mineral metabolism A more specific description of tissue growth is required to include stimulation of skeletal muscle growth We suggest inclusion of the following sentence from the current genotropin SPC to reflect influence of GH on overall body composition: "GH maintains a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat." Page 1, Paragraph 3 We would suggest adding in a comment after the "….hypopituitarism can also occur as part of combined or multiple pituitary deficiencies … add due to idiopathic or organic causes, or as a consequence of traumatic brain injury".	Scoping documents are normally brief. No action required.

Section	Consultees	Comments	Action
	Royal College of Nursing	This is accurate.	Comment noted.
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	The document should mention idiopathic short stature (ISS) as now a licensed indication in the USA. Currently the SHOX indication and SGA indication are often used to treat this group, in the presence of normal GH levels, normal chromosomes and short stature.	Technologies are appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for idiopathic short stature (ISS).
	Turner Syndrome Support Society [UK] [TSSS]	As regards TS, reasonably accurate.	Comment noted.
	Merck Serono	We believe this is defined appropriately.	Comment noted.
The technology/ intervention	Ipsen Limited	Same as above. Agree with the indication stated for children and for adults as stated above.	Comment noted.
	Novo Nordisk Ltd	Page 3, 2nd bullet – please change to: • growth disturbance (current height SDS -2.5 and parental adjusted height SDS <-1) The product manufactured by Novo Nordisk is called Norditropin SimpleXx.	The draft scope had been up-dated following a previous consultation. No further amendments required. The draft scope had been up-dated following a previous consultation. No further amendments required.

Section	Consultees	Comments	Action
	Pfizer Limited	Page 3, Table and text. We have a general comment regarding the biosimilar product Omnitrope. The table and accompanying text summarising indications for each of the somatropin licences does not reflect the key difference for the Omnitrope licence (compared to the other somatropin preparations). Namely that the clinical evidence base comes from data from only one study population, idiopathic GHD. This particular point was raised in the following recent review published by Pavlovic et al., part of the scientific advice unit of the French Regulatory Agency Affsaps (Pavlovic et al., Horm Res. 2008;69(1):14-21. 2007 Dec 4.) Pavlovic et al., particularly commented on whether the efficacy could be extrapolated from GH-deficient to non-GH-deficient states? They considered that it could have been reasonable to require data from at least two conditions, one being GH deficient and one non-GH deficient condition such as Turner syndrome. We feel that it is Important that the public and clinicians are aware of the biosimilar nature of Omnitrope.	The indications listed for each product in the scope are taken from their respective summary of product characteristics (SmPC). Guidance issued by the Institute states that technologies are recommended within their licensed indications which means that practitioners should use the SmPC to identify particular instructions for use. No change required to the scope.
	Royal College of Nursing	Yes	Comment noted.

Section	Consultees	Comments	Action
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	See above regarding SHOX and ISS, GH products should be used interchangeably in respect of patient choice, not in regard to license given to company. There is no mention of the range of devices or whether GH should be injected or transjected	Technologies can only be appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for idiopathic short stature (ISS). The remit of the appraisal is to appraise the clinical and cost effectiveness of human growth hormone (somatrpin). The appraisal of the devices for administering somatropin is outside the remit of the appraisal. Scope amended to include method of administration.
	Turner Syndrome Support Society [UK] [TSSS]	Yes	Comment noted.
	Merck Serono	Yes	Comment noted.
Licensing issues (only for manufacturers to complete)	Novo Nordisk Ltd	Commercial in confidence information removed	Comment noted.
	Merck Serono	No further licenses are currently pending	Comment noted.

Section	Consultees	Comments	Action
Population	Ipsen Limited	In children – population is defined appropriately. In adults – population is not included	For children, the definition of the population was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop. Human growth hormone as a treatment for growth failure in adults is outside the remit of this appraisal.
	Merck Serono	We believe this is defined appropriately	The definition of the population was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Pfizer Limited	Transition patients need to be included in this section. The current NICE paediatric guidance, issued in June 2003 includes some wording on transition but is quite vague. The ESPE consensus guidelines recommend a joint approach between both paediatric and adult endocrinologists in managing such patients. These guidelines recommend the retesting of patients and continuation of growth hormone treatment in patients with adult growth hormone instigated by paediatricians. Therefore, it would seem appropriate to include this population in the paediatric and adult guidance. The SmPC for genotropin was recently updated to include transition patients in November 2007 with the following wording: Section 4.1 Childhood Onset: Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a pituitary/hypothalamic disease or insult, an IGF-I SDS < –2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD. All other patients will require IGF-I assay and one growth hormone stimulation test. Section 4.2 Where childhood onset GHD persists into adolescence, treatment should be continued to achieve full somatic development (e.g. body composition, bone mass). For monitoring, the attainment of a normal peak bone mass defined as a T score > –1 (i.e. standardized to average adult peak bone mass measured by dual energy X-ray absorptiometry taking into account sex and ethnicity) is one of the therapeutic objectives during the transition period. .	The definition of the population was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop. Comment noted. Comment noted.

Section	Consultees	Comments	Action
		The inclusion of transition into this guidance, would ensure alignment with the DOH good practice guide, March 2008 “Transition; Moving on well”.	The scope has been amended to include consideration the transition of care from paediatric to adult endocrine services of young people whose linear growth is not complete. See ‘Other considerations’ in the table on page 5 of the final scope.
	Royal College of Nursing	Could there be potential for children with Noonan Syndrome to be considered?	Technologies are appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for Noonan Syndrome.

Section	Consultees	Comments	Action
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	The document should mention ISS. SHOX should be “as confirmed by DNA analysis” – but the availability of this test is very limited and genetics labs will often not send off for this test. This document should include other unlicensed uses such as in skeletal dysplasias?	Technologies are appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for idiopathic short stature (ISS). The scope has been amended. Technologies are appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for skeletal dysplasias.
	Southampton Health Technology Assessments Centre	Can NICE clarify whether children are defined as being under 16 or 18 years old? The proposed population is heterogeneous and would be difficult to include in a single review. 1) SHOX deficiency is linked with short stature in a variety of syndromes, but is not in itself a disease. There are also implications for genetic testing – how routinely is this done? Inclusion of people with this deficiency as a specific group therefore seems inappropriate. 2) As stated in the scope, children can be born small for gestational age (SGA) for a variety of reasons, and this is not linked to any specific disease. Children with SGA sometimes have other metabolic abnormalities, creating a heterogeneous patient group	The definition of the population was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Turner Syndrome Support Society [UK] [TSSS]	Is the population defined appropriately? Yes Are there groups within this population that should be considered separately? No	Comment noted. Comment noted.
Comparators	Ipsen limited	Yes	Comment noted.
	Royal College of Nursing	Potentially can use growth monitoring of height and weight, and also serum IGF-1 levels	The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
	Merck Serono	Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process, characteristics, raw material used, molecular characteristics and therapeutic mode of action. Results of appropriate tests should be provided in order to fulfil the requirements related to safety (pre-clinical tests) or to efficacy (clinical tests) or to both. Therefore, when choosing a comparator the same level of pre-clinical and clinical trial in the indication appraised should have been developed by the manufacturers in order to compare both efficacy and safety (including long-term) of the different medicinal products	The EMEA has approved the indications for each of the technologies being appraised. The indications listed for each product in the scope are taken from their respective summary of product characteristics (SmPC).

Section	Consultees	Comments	Action
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	The standard comparator is no treatment based on historical data. Growth monitoring is not a suitable comparator as it is ethically unacceptable not to treat children who would otherwise gain significantly from this technology in its licensed indications. Growth monitoring as currently practiced cannot be used as a standard comparator. It is often performed by poorly trained staff with poor equipment, and coverage is patchy, raising the issue of equality of access to treatment. One measurement at 5 will miss 40% of girls with Turner syndrome even if made universal and quality improved.	The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
		The effect of therapy started at different ages should be considered.	Guidance on the optimal age for initiation of therapy is considered too broad for this appraisal and falls outside of the remit for this appraisal.
	Southampton Health Technology Assessments Centre	The scope lists 'no treatment' as the comparator. Can NICE provide some clarification of this? Would growth monitoring also be an appropriate comparator?	The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
Outcomes	Ipsen Limited	Yes	Relevant outcomes were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
	Novo Nordisk Ltd	Please include bone mass and bone mineral density as outcomes. Please include body composition as an outcome for Turner Syndrome as well.	These have been added to the scope under 'outcomes.'

Section	Consultees	Comments	Action
	Pfizer Limited	The outcomes listed will capture the most important health benefits, however we would suggest the following additional outcomes capturing potential beneficial effects on metabolism, which is more relevant with transitional treatment and SGA: - glucose tolerance / insulin sensitivity - effects on lipid profile – LDL / HDL cholesterol, triglycerides - bone mineral density / bone mineral content	The scope has been amended.
		Quality of life (QoL) The measurement of quality of life in children is associated with a number of issues (for example, lack of adequate methods, different ages of children investigated, different areas of QoL in different ages) and therefore there is a paucity of data in this area. There is a lack of data to support the inclusion of health related quality of life (QoL) as a primary outcome of GH therapy. The lack of QoL data may present certain challenges when undertaking the economic modelling.	The limited health related quality of life data available was acknowledged at the scoping workshop. However, it was agreed that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
		For all GH indications, the goal of treatment, regardless of the underlying aetiology, is improved growth, improved stature and normalization of body composition. These can be easily measured and monitored by clinicians to evaluate the efficacy of treatment and assess the overall risk/benefit of the intervention in both the individual patient as well as in groups of patients. Improvement in growth, stature and body composition are the direct result of GH treatment and are strictly dependent on the biological actions of GH.	Comment noted.
	Merck Serono	We believe this is defined appropriately.	Comment noted.
	Royal College of Nursing	Yes	Comment noted.

Section	Consultees	Comments	Action
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	Outcome measures in children differ from adult patients and measures should be weighted in the following order. change in actual height velocity (centimetres/year). Standard deviation scores in height velocity are meaningless in individual cases. height standard deviation score relative to the distribution of height in children of the same chronological age (NOT bone age). (final) adult height and height gain. improvement in body composition for GHD and PWS (BMI, lean mass, % body fat). adverse effects health related quality of life (not a primary outcome endpoint in children and still under research). QoL data is currently very limited (National trial in progress, but results will not be ready for NICE timescale).	Relevant outcomes were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Southampton Health Technology Assessments Centre	These seem to be appropriate measures. However, not all of these outcomes may be available for all of the conditions to be considered in this review. This will be particularly important if the MTA limits the inclusion criteria to RCTs, which do not often report the ideal measure of Final Height. Quality of Life is now listed as the first outcome measure – does this imply that it should be the primary outcome measure in trials?	The Institute recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. See the technology appraisals methods guide: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf Relevant outcomes were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop. Outcomes in the scope are not listed in order of importance.
	Turner Syndrome Support Society [UK] [TSSS]	Yes	Comment noted.
Economic	Ipsen Limitd	No further comments	Comment noted.

Section	Consultees	Comments	Action
analysis	Pfizer Limited	We appreciate that a cost per QALY output is generally required by NICE when Technology Appraisals are undertaken. However, since it is widely acknowledged that quality of life data is not routinely measured in HGH trials involving children there is a paucity of data (as stated above). Therefore a pragmatic approach to modelling, including the need to look for alternative data sources to support the model, will need to be considered.	The limited health related quality of life data available was acknowledged at the scoping workshop. However, it was agreed that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.
	Merck Serono	Given that Somatropin is the same medication with several manufacturers holding marketing authorisation, then cost minimisation analyses may be more appropriate than cost utility analyses.	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See the technology appraisals methods guide: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	Cost utility analysis may be considered in terms of height improvement along with associated incremental cost per quality adjusted life year where data exist. See above comments re QoL data Many of the subtler effects of GH such as those on quality of life, bone mineral density or side-effects may not have implications until later adult life so some sort of view on the collection and analysis of longer term follow-up data over decades needs to be made	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Comment noted.

Section	Consultees	Comments	Action
	Southampton Health Technology Assessments Centre	The original economic model for this review used cost/cm gained as an output. It would be difficult to translate this into cost/QALY, unless more QoL data has become available since the last review. An additional consideration will be consistency of outcomes across groups. There may be QoL data for some conditions but none for others, in which case cost/QALY cannot be calculated fairly for all patient groups/conditions. If life expectancy is different for the identified conditions, this would require separate models for calculation of cost/QALY. This would have an impact on the workload, and it may not be feasible to calculate this (even where QoL data exist) for all the specified conditions within the resources for this project). As SGA would be hard to define, it might be difficult to populate an economic model with suitable data. Also, it might not be sensible to aggregate all the possible causes for the different conditions onto the same model if key patient characteristics differ.	The limited health related quality of life data available was acknowledged at the scoping workshop. However, it was agreed that cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The complexity of the appraisal will be taken into account when developing the timelines for the appraisal. Comment noted.
	Turner Syndrome Support Society [UK] [TSSS]	The time horizon for the benefit of added height is the life time of the individual	The time horizon of the economic analysis is not defined in the scope but will be considered as part of the appraisal.
Other	Ipsen Limited	No further comments	Comment noted.

Section	Consultees	Comments	Action
considerations	Pfizer Limited	We would recommend that this re-review considers the contribution that an Observational Database can make to this re-review (for example, treatment outcomes and safety data on substantial numbers of patients). Longstanding databases such as those in growth hormone therapy with up to 20 years prescribing experience in 60,000 patients aid clinicians and Trusts in fulfilling their obligations to monitoring and clinical governance as set out in the Children's NSF (medicines for children and young people).	The Institute recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. See the technology appraisals methods guide: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
		We would also recommend that the Value Added Services which Manufacturers can offer (for example, the dedicated support service that can be offered to help healthcare professionals, patients and their carers to manage their treatment) are considered. "Education is thought to be an important factor in encouraging compliance and thus increasing the likelihood of achieving treatment goals. Ref Rosenfeld and Barker (Endocr Pract. 2008 Mar;14(2):143-54)"	Comment noted.
		We would recommend that the importance of patient choice in improving patients' compliance is considered. (Kapoor et al Arch. Dis. Child 2008 Feb;93(2):147-8)	Comment noted.

Section	Consultees	Comments	Action
	Merck Serono	**How SGA should be defined?** The Royal College of Obstetricians and Gynaecologists define SGA as follows: "SGA refers to a fetus that has failed to achieve a specific biometric or estimated weight threshold by a specific gestational age. Various thresholds (2.5th, 3rd, 5th, 10th, 15th and 25th centiles and 1.0, 1.5 or 2.0 standard deviations below the population average) are used for various fetal measures. The commonly used threshold is the tenth centile for abdominal circumference and estimated birth weight. SGA fetuses are a heterogeneous group comprising fetuses that have failed to achieve their growth potential (fetal growth restriction, FGR) and fetuses that are constitutionally small. Approximately50–70% of fetuses with a birthweight below tenth centile for gestational age are constitutionally small, and the lower the centile for defining SGA, the higher the likelihood of FGR. On the other hand, a fetus with growth restriction may not be SGA." This was consistent with a review of the literature and the inclusion criteria of our key clinical trials. http://www.rcog.org.uk/resources/Public/pdf/Small_Gest_Age_Fetus_No31.pdf **Whether growth monitoring should be included as a standard comparator**? Growth monitoring should be included as a standard comparator as it is the best way of determining the efficacy of growth hormone treatment	The definition of Born small for gestational age (SGA) was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop. The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	SGA is defined as birth weight and/or length below minus 2 SD from the mean adjusted for gestational age – international consensus statement: P. E. Clayton, S. Cianfarani, P. Czernichow, G. Johannsson, R. Rapaport, and A. Rogol **Management of the Child Born Small for Gestational Age through to Adulthood: A Consensus Statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society** J. Clin. Endocrinol. Metab., Mar **2007**; 92: 804 - 810. Issues requiring special attention to eliminate unlawful discrimination and promote equality: The discrepancy between licensed indications for GH treatment (above) and current NICE guidance should be addressed by this review. There is in the UK currently a lack of a satisfactory growth monitoring programme which allows children with the above disorders to be identified completely within the child population and therefore obtain optimal treatment at a suitably young age, thus maximising the cost-utility gain for this technology. Current estimates are based on less than optimal treatment regimens. It is important that the document at least considers ISS. It is likely that an EC license will be granted in next few years and would be a pity if we had the same situation as currently with IUGR indication where licensed indication but no NICE guidance.	The definition of Born small for gestational age was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
	Royal College of Pathologists	* GH is licensed for use in the USA for Idiopathic Short stature but not in the UK. In practice, children are treated by citing a possible underlying genetic mutation as a cause of the short stature. A license is likely to be granted for use in ISS in the next couple of years, NICE should consider indications for use in these patients now.	Technologies are appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for idiopathic short stature (ISS).
		* In practice growth measurement and monitoring in the UK is woefully inadequate and needs to be improved to ensure equity of access to treatment if this is to be a qualifying criteria.	The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
		* Mutations in the homeobox gene SHOX are cited as a justifiable and licenced use for GH but access to mutational analysis is patchy with some Trusts denying access to testing on the basis of cost.	Comment noted.
		* Quality of life improvements produced by the use of GH in ISS are poorly researched and it seems reasonable that better data could be used to guide the recommendations made by NICE in this contentious area	Technologies are appraised according to their marketing authorisation. Currently there is no UK market authorisation for the use of human growth hormone (somatropin) for idiopathic short stature (ISS).

Section	Consultees	Comments	Action
Any additional comments on the draft scope	Novo Nordisk Ltd	How should SGA be defined? We would propose using the SGA definition from Clayton et al (2007), which uses weight and/or length less than -2SD. Clayton PE, Cianfarani S, Czernichow P et al. Consensus statement: Management of the child born small for gestational age through to adulthood: A consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. JCEM 2007 92(3):804-810 Whether growth monitoring should be included as a standard comparator? It is our understanding that for patients with TS and CRI, height will be monitored as part of their routine follow-up. Patients with GHD and small children born SGA will not routinely have their height monitored unless they are being treated with growth hormone. Therefore, growth monitoring should be used as a standard comparator in TS and CRI but not in GHD and small children born SGA. Any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality? The current NICE guidance states, 'GH treatment should be re-evaluated and normally discontinued if there is a poor response to treatment, defined as the increase in growth velocity of less than 50% from baseline, in the first year of therapy. Ongoing response should be evaluated against expected growth based on standard growth charts. Therapy should be normally stopped when final height is approached and growth velocity is less than 2 cm total growth in 1 year. Persistent and uncorrectable problems with adherence to treatment should also be taken into account as part of re-evaluation of treatment. In Prader-Willi syndrome evaluation of response to therapy should also consider body composition.'	The definition of born small for gestational age (SGA) was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop. The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop. Comment noted.

Section	Consultees	Comments	Action
		The need for a long-term commitment to daily subcutaneous injections has major implications for the child and the family. An objective assessment of prescription data in a regional clinic setting (Kapoor et al 2007) revealed a high prevalence of poor concordance with growth hormone therapy. Specifically, they reported lower concordance being associated with longer duration on growth hormone therapy ($p<0.005$), lack of choice of delivery device ($p<0.005$) and short prescription durations ($p<0.005$). Critically, they also reported a predicted lower height velocity ($p<0.05$) with lower concordance, therefore highlighting that choice is clinically important. Furthermore, Ahmed et al (2007) reported that every patient has different preferences and needs. Thus, informed choice of about matters such as the reconstitution of the growth hormone, the storage flexibility of the growth hormone, the device, and availability and scope of home care services should be clearly communicated to all patients who are to start growth hormone treatment. In addition, a treatment re-evaluation of those patients already on growth hormone who did not get a choice of brand (and who may now have different needs), who are at a higher risk of non-compliance due to the length of time they have been on treatment, should be undertaken perhaps after 1 - 2 years of treatment. Kapoor RR, Burke S, Sparrow S et al. Monitoring of concordance in growth hormone therapy. Arch Dis Child. 2008 Feb;93(2):147-8 Ahmed SF, Blamires C, Smith WA. Facilitating and understanding the family's choice of injection device for growth hormone therapy by using conjoint analysis. Arch Dis Child. 2008 Feb;93(2):110-4.	Comment noted.

Section	Consultees	Comments	Action
	Pfizer Limited	Response to questions- How SGA should be defined? SGA definition will have to be that from SPC i.e. -2sd at birth and -2.5sd and parental adjusted height -1 SD at time of treatment start.	The definition of born small for gestational age (SGA) was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
		Whether growth monitoring should be included as a standard comparator? Growth monitoring is vital in someone on GH Rx and so should be a comparator	The comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
		Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality? Need to be aware that Turner's patients are uniquely vulnerable group with clear health and behavioural difficulties before height taken into account. Also discriminating against this group would be inter alia sex discrimination	Comment noted.
		Also, it is important to note that SGA children are disproportionately born to young mothers with less social support and lower socio-economic status who may not be as able as more wealthy mothers to access health services. This could result in a health inequity as this group of patients are potentially more disenfranchised from seeking appropriate support and treatment.	Comment noted.
		It may also be worth exploring the inequality that may exist between males and females receiving treatment with human growth hormone. An analysis of the KIGS observational database supports the statement that girls are under-represented in the overall patient cohort treated with human growth hormone.	Comment noted.

Section	Consultees	Comments	Action
	Royal College of Nursing	The table is not clear on which product is licensed for which indication.	The table has been amended to improve clarity.
		Re-wording is needed under 'Current NICE guidance point 5': Many GPs misconstrue this as the Paediatric Endocrinologist having to write the first prescription, and some even thinking that the Paediatric Endocrinologist has to give the first injection. Many hospitals have to prescribe the first few months of GH.	The wording of the existing NICE guidance cannot be amended following its publication.
		RE: GH discontinuation: re-wording is needed, as some patients make transition into adult endocrine clinics.	The wording of the existing NICE guidance can not be amended following its publication.
		SGA description: ?utilise the description within the NESGAS study: www.bsped.org.uk/professional/projects.sga.htm	The definition of born small for gestational age (SGA) was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

Section	Consultees	Comments	Action
		Since this original proposal, research has been undertaken regarding management of girls with Turner syndrome. This needs to be considered.	Guidance on the management of girls with Turners syndrome is considered too broad for this appraisal and falls outside of the remit for the appraisal.
		Research has been undertaken and is ongoing regarding GHT for children with SGA. We consider that this evidence needs to be included in the discussion.	Comment noted.
		Review of the use of GHT in children with Prader-willi syndrome and monitoring	Comment noted.
	British Society for Paediatric Endocrinology and Diabetes/Royal College of Paediatrics and Child Health	The definition of SGA should be as follows 'Less than -2SD at any gestational age seems the most appropriate as already used to approve the use of GH in the SGA group.'	The definition of born small for gestational age (SGA) was discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.
	Southampton Health Technology Assessments Centre	The consultees' responses to NICE's questions for consultation will provide useful clarification for the review. In particular we would welcome further definition of SGA and also the use of growth monitoring and other potential comparators in clinical practice.	Consultees' responses have informed the development of the final scope. The definition of born small for gestational age (SGA) and appropriate comparators were discussed at the scoping workshop. The scope has been amended to reflect what was agreed at the scoping workshop.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

NHS Quality Improvement Scotland
Eli Lilly and Company Limited
Department of Health
Ferring Pharmaceutical
Welsh Assembly Government