Health Tech Asmnt Act. 2019 April; 3(1).e5848 doi: 10.18502/htaa.v3i1.5848.

Published online 2019 April 05. **Research Article**

Cost-effectiveness of Growth Hormone and its Consumption Indications: A Systematic Review of Economic Evaluation Studies

Mohsen Pakdaman [1], Fahimeh Golmakani [2, *], Hamid Reza Dehghan [2], Reza Valagohar [3], Akram Beik Yazdi [4], Mahdiye Namayande [5]

[1] Department of Health Care Management, Health Policy and Management Research Center, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Department of Health Technology Assessment, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Health Insurance Organization, Yazd, Iran
[4] Alavi Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[5] Department of Biostatistics and Epidemiology, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

* *Corresponding author:* Fahimeh Golmakani, Department of Health Technology Assessment, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Tel: +98-9352383148, Email: golmakanifi@mums.ac.ir

Received 2019 March 21; **Accepted** 2019 April 02.

Abstract

Context: Growth hormone deficiency (GHD) is one of the main reasons for short stature in children, which can be treated by early diagnosis. Stature is an appropriate measure to assess a child's overall growth and health, and one's height can affect his psychosocial and social well-being. Human growth hormone (HGH) has extensive effects on biological processes as well as height. Due to the high cost of growth hormone (GH) drugs, in most countries GH is prescribed according to scientific indications.

Methods: The present study was a systematic review, which examined PICOD- based case studies published from the beginning of 2002 to February 2019 on Web of Science, PubMed, Scopus, SID, Embase, and Magiran databases in the field of health technology assessment and the economic evaluation. According to the inclusion criteria, 11 relevant articles were selected in the present study.

Results: The findings showed that GH therapy was effective in increasing patients' quality of life, and that the growth rate of children treated with GH was more than 2.5 cm per year, in comparison to the control group. Furthermore, the results of the studies indicated the cost-effectiveness of GH since the cost of each centimeter height increase in children was on average US $20,000, and the incremental cost-effectiveness ratio varies based on QALY's criteria in studies for various indications (Turner syndrome, idiopathic short stature, growth hormone deficiency, Prader Willi syndrome, Infants small for gestational age (SGA), chronic renal failure (CRF) and (SHOX-D). The highest cost efficacy per QALY was for growth hormone deficiency (from £20,000 to £30,000), and the lowest cost efficacy is for Prader Willi (from £55,000 to £135,000).

Conclusions: Studies showed that GH increases the height of the children treated with GHD, compared to the control children; hence, the use of growth hormone is recommended after doing the experiments for all children with GHD. This issue can be considered by health policy makers to implement in healthcare programs.

Keywords: Children's Stature; Cost-Effectiveness; Growth Hormone; Growth Hormone Deficiency Treatment; Incremental Cost-Effectiveness Ratio; Quality of Life; Somatotropin

1. Context

Growth hormone deficiency is one of the main reasons of short stature in children treated with early diagnosis. Height is considered as an appropriate measure in assessing a child's overall growth and health, and stature affects one's psychosocial and social well-being (1). Individual and collective health is certainly the most important aspect of life to be achieved by human beings (2). The human growth hormone (HGH) is produced in the pituitary gland, has huge effects on biological processes, including fat and carbohydrate metabolism, bone growth, and causes the ultimate height in adults. Growth hormone (GH) is a polypeptide hormone composed of 191 amino acids in a long chain, whose secretion by the pituitary gland is influenced by the hypothalamus gland as secreting the growth hormone releasing hormone (GHRH) causes the secretion of the GH from the pituitary gland. Moreover, the hypothalamus gland prevents the secretion of GH by secreting somatostatin (3). The secretion of GH from the anterior pituitary is regulated by the stimulating and inhibiting peptides of the hypothalamus, GHRH, and the inhibiting hormone to release somatotropin (somatostatin). This hormone is secreted throughout one's lifetime and has important physiological impacts even after maturity (4).

The GH secretion follows an oscillating pattern; therefore, its random measurement is valueless. Furthermore, some cases, including liver failure and cirrhosis, excessive hunger, anxiety, diabetes Type I, and acute illness, increase

the secretion of this hormone. Therefore, measuring the level of IGF-1 (insulin-like growth factor-1) is a better criterion for assessing the activity of this hormone since its level does not change during a day. Growth hormone deficiency (GHD) occurs during infancy and childhood in the form of growth retardation, shortness of stature, and decreased fasting glucose levels. Adult GHD syndrome may increase with increased abdominal fat, decreased power and capacity of activity, reduced BMI, and increased body fat percentage and psycho-social disorders. Adult GHD is often associated with other hypopituitarism symptoms (5). There are a number of medical conditions such as non-functional pituitary adenoma (NFPA), functional adenoma, craniopharyngioma, brain malignancy, brain injury, acromegaly, idiopathic hypopituitarism, Sheehan's syndrome, pituitary tumors, pituitary abscess, lymphocytic hypophysis, and others, leading to causing GHD (6). Pituitary injury induced by radiotherapy or surgical intervention in some patients reduces the production of GH. A study in the UK shows that the GHD prevalence is 1 in 2700 adults and between 1 in 3500 and 1 in 4000 children (7). Generally, GH treatment in children is safe. Some common side effects resulting from mild to moderate GH therapy include headache, muscle or joint pain, mild hypothyroidism, swelling of the hands and feet, scoliosis, and gynecomastia. Some rare but dangerous symptoms of such a treatment include severe headaches with vision impairment and problems in the hip joint since the upper part of the femur is removed from the site and pancreatitis. the advantages of GH are more than its potential risks (8), even though, the side effects of this hormone are extremely rare and it is considered a safe drug (9). Currently, therapeutic indications have increased in children and even adults (10).

Somatotropin and somatoma are two forms of GH, which use the recombination DNA technology. These products are useful in GHD treatment for both children and adults (11). Due to the high cost of the drugs, most countries have indications to use them. FDA-approved growth hormone indications include (A) children with advanced kidney disorders such as chronic renal failure (CRF) or end-stage renal tumors, who are candidates for kidney transplantation; (B) Idiopathic short stature; (C) Prader Willi syndrome (In this syndrome, growth disorder is common in the first year of life and is followed by excessive obesity with short stature and multiple fingers); (D) Turner syndrome (girls who have one X chromosome less than others and their karyotype is X0); (E) Noonan syndrome; (F) AIDS progressive syndrome; (G) short bowel syndrome; (H) after kidney transplantation; and (I) SGAGH in children mainly to increase their growth. However, they are basically used based on its anabolic effects in adults (12). In the present study, considering that GH and its consumption indications have different costs and consequences, a systematic review of the cost-effectiveness of GH and its consumption indications was carried out, and the results were presented to policy makers to be adopted in decision making and planning processes.

2. Methods

2.1. Objectives

This systematic review study aimed to examine the cost-effectiveness of GH and its consumption indications.

2.2. Searching Method

First, the main electronic English databases, including MEDLINE (PubMed), Scopus, Cochrane, Web of Science, CRD, PubMed, Embase, DARE, CDSR, HTA, and Clinical Key, and Persian databases (namely Irandoc, Magiran, and SID) were searched using a special search strategy for the papers published from the beginning of 2002 to June 2018. Health assessment and evaluation studies including all clinical trials (CCT and RCT) were examined. Considering the costs and cost-effectiveness of the GH drug and its consumption indications, the studies conducted considering QALY (quality-adjusted life year or quality-adjusted life-year) to evaluate the cost-effectiveness ration were included. The search strategy was performed according to the keywords and the structured question using 'AND' and 'OR' operators. The following Persian keywords were also used during the searching process: Children's stature, cost-effectiveness, growth hormone, growth hormone deficiency treatment, incremental cost-effectiveness, life quality, and somatotropin. In this regard, English keywords were as follows: growth hormone, cost-effectiveness, cost utility costing, growth hormone deficiency, somatostatin, children, safety, growth hormone, short, treatment with GH, economic evaluation, growth hormone, somatotropin, economic assessment, incremental cost-effectiveness ratio, and quality of life.

2.3 .Qualitative Assessment of Studies

The quality of the concerned studies was assessed according to the CHEC checklist (consensus on health economics criteria checklist). The checklist contains 20 questions assessing the studies in terms of population descriptions, economic relevance of study, validity of methodology and model, equality cost with the physical unit, cost-effectiveness, results of studies, ethics, and follow-ups. Each study was scored from 1 to 12 according to the concerned questions. Based on a specified criteria, the score of each study represented the study quality (13).

2.4 .Inclusion and Exclusion Criteria

All studies on economic evaluation, health technology evaluation, and clinical studies, which have somehow addressed the costs and consequences of GH, were included in the present study. Due to the limited research simultaneously examining the outcome, cost, and cost-effectiveness, the final studies that examined only one or

both aspects of GH were included in the study. Moreover, only those articles that examined the use of GH were included in the study, and studies that emphasized only on or cost-effectiveness or outcome of GH were excluded. Furthermore, given the limited number of resources and shortage of time, only English and Persian articles were used, and the articles published before 2002 were also excluded (Figure 1).

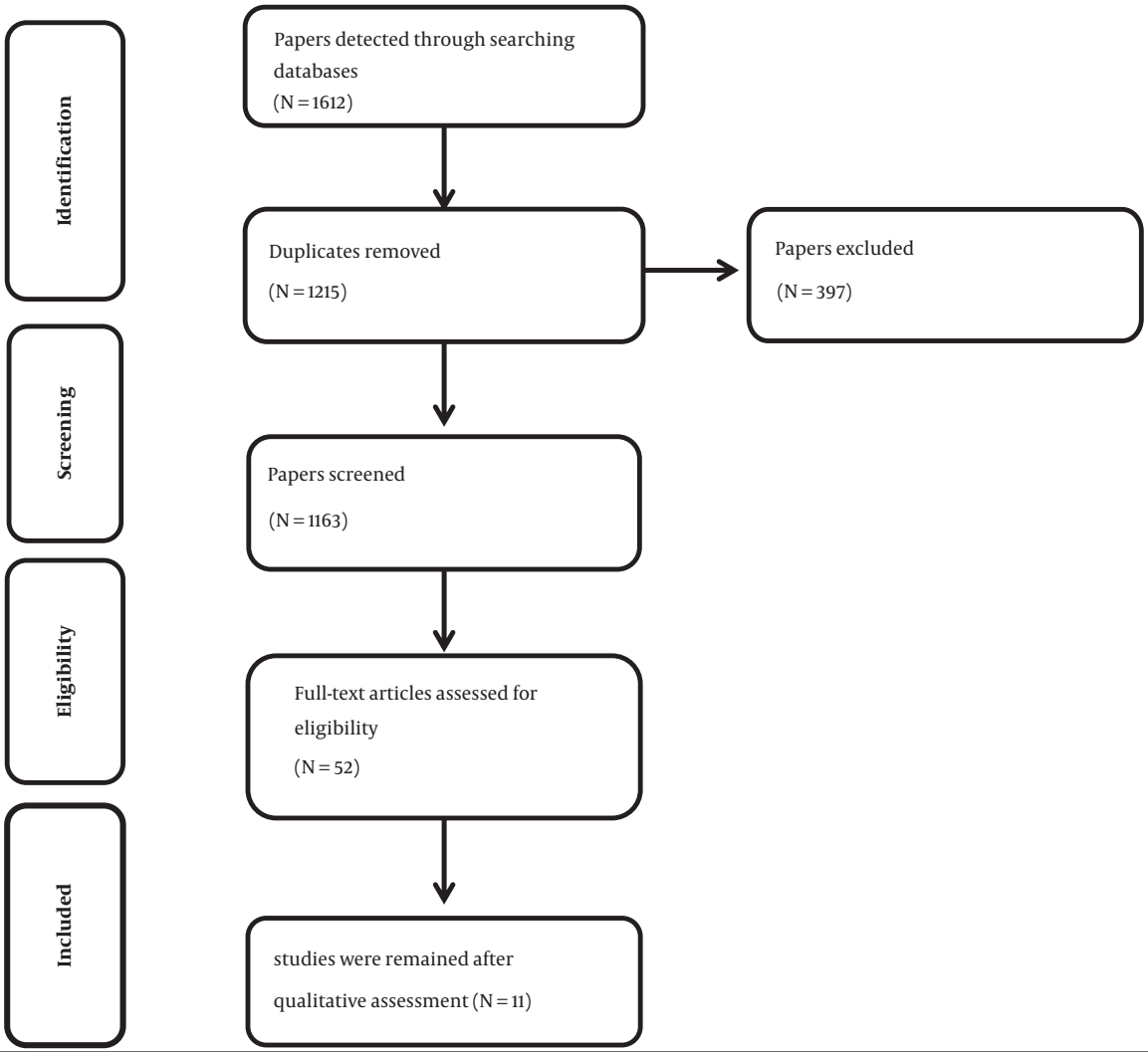

Figure 1. The study procedure according to PRISMA standard

2.5. Study Selection

The present study was carried out in accordance with PRISMA principles. First, the titles and abstracts of the included articles were investigated. Then the text of the articles was studied. In all the steps of selecting studies, two separate researchers were involved, and the cases of inconsistency were resolved by discussion to reach an agreement. In the next step, the articles meeting the inclusion criteria were selected and evaluated qualitatively.

2.6. Data Extraction

After extracting the data from the studies, the data were arranged by author's name, year of study, type of indication, outcomes, costs, and cost-effectiveness.

2.7. Data Analysis

Given the heterogeneity in the results of the studies and the techniques of economic evaluation, the meta-analysis was not possible; therefore, the qualitative method was utilized to analyze the collected data.

3. Results

3.1. Study Selection

A systematic review of the databases was conducted based

on the inclusion and exclusion criteria, and 1612 articles were obtained. After removing 397 duplicate studies, 1215 articles were categorized by their titles. The titles of the articles along with their abstracts were reviewed. The abstracts of the remained articles were re-examined, throughout which 1163 articles were removed in this step. Then the other 52 remained articles were included in the abstract screening step to extract the final studies. The full texts of these articles were reviewed by the first researcher based on the inclusion and exclusion criteria. In the case of ambiguity, the second researcher re-conducted the review process. Finally, 11 articles were included the final step of the study. The study selection process was performed based on PRISMA protocol.

3.2. Data extraction

In this review study, we had one study published in 2018, two studies published in the last three years (2016), one study in the past eight years (2011), four studies in nine years ago (2010), one study in the past ten years (2009), and one study published in the past seventeenth years (2002). Among the included studies, there were five systematic review studies, three cohort studies, three clinical trials, and one cross-sectional study. one of them was conducted in 2008; while the others were carried out in 2010 which were done on different indications. One of the review studies in Iran was in Persian, and the other studies were in English. Tables 1 and 2.

Table 1. Outcomes, Costs, and Cost-Effectiveness of GH According to the Systematic Review Results

Authors' names	Indication						GH Cost	Outcomes	Cost-Effectiveness
	Turner	SGA	Prader Willi	Growth Hormone Deficiency	Short Stature Without cause	SHOX-D CRI			
Bryant (8)	*		*	*	*		The cost of GH treatment for a child varies from 4310000 - 530000 (for GHD) to 55,500 - 83,000 pounds (for PWS), compared to monitoring the normal growth.	An increase in the ultimate height for the treated children, compared to children who did not receive the GH, was 11 cm (GHD, 8 - 11 cm, TS, 5 cm, CRF, 3 - 9 cm, PWS, 10 - 11 cm, ISS 2 - 7 cm)	An incremental cost per centimeter of height gain is approximately 6,000 pounds for GHD, 16,000 to 170,000 pounds for TS, $7,400 to $2,400 for CRF, $1,300 - 500 to $2,700 for ISS, and possibly £7030 for PWS.
Vitova and Tichopad (14)				*			Sensitivity analysis showed that the ICER does not exceed the considered uncertainty of 50,000 CZK.	The hypothetical group consisted of 10,000 boys created 95017 incremental QALYs and 1.6 CZK additional costs over a lifetime horizon. A hypothetical group of 10,000 girls created 11504 incremental QALYs and 351 CZK of additional costs	Sensitivity analysis showed that the ICER does not exceed the considered uncertainty of 50,000 CZK.
Twena (15)		*					Throughout a patient's life, Somatropin (0.033 mg/kg/day) was associated life years with adjusted quality life years (QALYs) incremental costs of SEK 1,161,473, compared with non- treatment.	Somatropin (Norditropin®) was associated with an increased cost for QALY 372,861 versus non-treatment. The possible sensitivity analysis, where all parameters were different, showed that somatropin (Norditropin®) was more likely to be cost-effective, based on a willingness to pay SEK 600,000 per QALY.	Assuming the willingness to pay SEK 600,000 per QALY, somatropin (Norditropin®) is a cost-effective return strategy for SGA children in Sweden, which provides significant incremental health benefits at an additional cost.

Christensen (16)	*	*		4359 pounds per cm	At the beginning of the study, the patients' stature was 108.53 (13.19), which reached 167.87 (6.81) at the end of the study. HSDS was -3.12 (0.70) at beginning and reached (0.65) -1.14 at the end of the study.	The cost of the incremental cost-effectiveness of somatropin, compared to non- treatment with growth hormone, was £70263 with 2.95 QALY. The cost of the obtained incremental cost-effectiveness was £23807, which was below the UK threshold of 30,000. One-way sensitivity analysis indicated that the results were sensitive to changes in discount rates, early childhood height, and utility values. The probabilistic analysis also showed that somatropin was cost-effective in 68.74% of the simulations, given the threshold of willingness to pay £30,000 per QALY.
Christensen (17)	*	*		Total cost: SEK 424,786 (SEK 460,005) (Swedish krona) for children under treatment	The height of the children was 108.53 cm at the beginning of the study and 167.87 at the end of the study.	For children with short-term SGA, treatment with somatotropin was accompanied with an additional 3.29 QALYs and an additional cost of 792,489 SEK (Swedish krona) with no treatment. For GHD, treatment with somatotropin resulted in an additional 3.25 QALYs at an incremental cost of 391,291 SEK. This is equivalent to an incremental cost per QALY of SEK 240,831 and SEK 120,494 for SGA and GHD below the future cost threshold of 500,000 - 600,000 SEK/QALY, respectively. Somatotropin is a cost-effective strategy in Sweden for children with GHD and SGA.

Tasavon Gholamhoseini (18)			*		*		The medical treatment cost was 5,092,964,520 Rials, and the expenses of a health insurance organization in Kerman province was 71,175,443,448 Rials.	Increased height with and without GH treatment was 174.4 and.90, respectively.	The treatment of short stature in children by GH is cost-effective. The incremental cost-effectiveness ratios based on QALY's criterion and from the perspective of the patient and the health insurance organization were 743,133, and 9,846,567 Rials, respectively.
Bolin (11)			*				Direct costs for GH-treated male and female patients were 421851 SEK (44 405 EUR) and 544344 SEK (56 284 EUR), respectively, compared to untreated patients. One dollar is equall to 9.03 kr.	The treatment effects seemed to occur in the first year, the change in QoL-AGDHA in the following years was due to aging. Mortality risk: It was assumed to be different between age and gender groups; however, it was equal in the QoL-AGDHA government.	There was SEK 410974 (€43 260) in men and SEK500263 (€52 659) in women. The mean annual life expectancy was 3.4 (male) and 2.7 (female). Mean QALYs were 3.0 (men) and 2.8 (women). Apart from indirect costs, total ICER was 11390 SEK (14637 Euro) and 205850 Euro (21 668 Euro), respectively. The key determinants of outcomes, improved quality of life, increased survival, and costs of GH (genotropin) treatment were more cost-effective in adult patients with GHD, compared to Swedish informal thresholds, whereas the incremental cost in QALY was between 100,000 (10 526 Euro) and 500 000 SEK (6333 Euro 523).
Craig (19)			*				An average of 0.001 QALYs was obtained for an average of 21 pounds	The Grote strategy was both more expensive and more effective, with a mean cost of £68 and a mean QALY gain of 0.042.	The incremental cost-effectiveness ratio was £1144 per QALY gained. Under no scenario, the ICER exceeded £8000.
National Institute for Health and Clinical Excellence (20)	*	*	*	*	*		18 pounds per mg	The height obtained in centimeters for each indication was obtained as follows: GHD continued: 27.45, GHD = 27.45: Turner syndrome 7.95, CRI = 3.65, and SGA = 5.67	The incremental cost-effectiveness ratio (ICER (£/QALY) for each indication was obtained as follows: GHD continued: £20,673, GHD = £17,552, Turner syndrome £29,757, PWS = £32,540, CRI = £15,962, and SGA = £18,167

Takeda (10)	*	*	*	*		Each mg of growth hormone costed $20.70. The cost of increasing stature per cm is 2256 for those with GHD, 9540 for Turner Syndrome, 9001 for CRI, and $2467f or SGA.	The increased stature of younger children was 6.7 cm after two years. HtSDS values were significantly higher in the treated girls. PWS: Infants receiving RhGH for one year grew more significantly (6.2 cm) than those untreated. SGA: 3-year-old children with no growing were about 4 cm. SHOX-D: After two years of treatment, children were about 6 cm taller than the control group, and HtSDS was statistically significant in the treated children. During the one-year study period, they grew 2.7 cm faster and had higher standard deviation scores (-2.3 vs. -2.8) than untreated children.	GH deficiency with regard to the willingness to pay threshold was obtained to range from £20,000 to £30,000 per QALY. Prader-Willi Syndrome cost-effectiveness ratio (ICER) was obtained between £55,000 and £135,000 per QALY (depending on hypothesis), and the other conditions with ICER ranged between £33,000 and £40,500 for each QALY obtained. Incremental Costs Based on RhGH Estimated Annual Healthy Living (QALY), Compared to Untreated Treatment: £23,196 for GHD, £39,460 for TS, £135,311 for PWS, £39,273 for CRI, £33079 for SGA and £40531 for SHOX-D. The probability of treating any of the conditions at the cost of £30,000 was 95% for GHD, 19% for TS, 1% for PWS, 16% for CRI, 38% for SGA, and 15% for SHOX-D.
Christensen (6)						Cost per mg 234 SEK	For short children born SGA, somatropin treatment was associated with an additional 3.29 QALYs at an incremental cost of 792,489 SEK (Swedish Krona), compared to no treatment. For GHD, somatropin treatment resulted in 3.25 additional QALYs at an incremental cost of 391,291 SEK.	This equates to an incremental cost per QALY of 240,831 SEK and 120,494 SEK for SGA and GHD below a cost-effectiveness threshold of 500,000 - 600,000 SEK/QALY, respectively. Somatropin is a cost-effective treatment strategy in Sweden for children with GHD and SGA.
Christensen (17)						Cost per milligram: £21.39	Somatropin (0.033 mg/kg/d) treatment was associated with a height gain of 16.12 cm and a cost per centimeter of height gained of £4359, compared to non-treatment condition.	The incremental cost of somatropin treatment was £70,263, with a QALY gain of 2.95, resulting in an incremental cost per QALY of £23,807-below the widely accepted cost-effectiveness threshold in the United Kingdom of £30,000.

Table 2. Incremental Effectiveness Cost Ratio (ICER) for Each Indication

Title	First Author	Type of Study	Year of Publication	Currency	Incremental Effectiveness Cost Ratio (ICER) for Each Indication						
					Turner	SGA	Prader Willi	Growth Hormone Deficiency	Short Stature with No Cause	SHOX-D	CRI
Recombinant human growth hormone for the treatment of growth disorders in children: A systematic review and economic evaluation	Bryant (8)	Systematic review	2002	Pound	39460	33,000 and £40,500	£55,000 and £135,000	£20,000 -30,000	£20,000 -30,000	33,000 and £40,500	33,000 and £40,500
Cost-effectiveness of somatropin administration with Increased adherence due to monitoring compared to non-monitored administration in Patients with growth hormone deficiency	Vitova (14)	Cohort	2013	Czech koruna	-	-	-	CZK157,000	-	-	-
Economic evaluation of somatropin (Norditropin®) for the treatment of short children born SGA in Sweden	Twena (15)	Randomized clinical trial	2008	Swedish Krona	-	372'861SEK	-	-	-	-	-
Economic evaluation of somatropin (Norditropin) for the treatment of short children born small for gestational AGE (SGA)	Christensen (16)	Clinical Trial	2008	Tristan da Conha Pound	-	GBP26,794	-	-	-	-	-
Cost-effectiveness of growth hormone (somatropin) for the treatment of children with short stature	Tasavon Gholamhoseini (18)	Cross-sectional research	2018	Iranian Rial	-	-	-	9,846,567	-	-	-
The cost-effectiveness of growth hormone replacement therapy (Genotropin®) in hypopituitary adults in Sweden	Bolin (11)	Cohort	2013	Euro	-	-	-	€15,975 and €20,241	-	-	-
Growth monitoring for short: Update of a systematic review and economic model	Craig (19)	Systematic review	2011	Pound	-	-	-	£1144	-	-	-
Human growth hormone (somatropin) for the treatment of growth failure in children	National Institute for Health and Clinical Excellence (20)	Systematic review	2010	Pound	£29'757	£18,167	£32'540	£17'552	£20,673	-	£15,962

Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation	Takeda (10)	Systematic review	2010	Pound	£39,460	£33,079	£135,311	£23,196	£23,196	£40,531	£39,273
The cost-effectiveness of somatropin treatment for short children born small for gestational age (SGA) and children with growth hormone deficiency (GHD) in Sweden	Christensen (17)	Cohort	2010	Krona	-	240,831 SEK	-	120,494 SEK	-	-	-
Cost-effectiveness of somatropin for the treatment of short children born small for gestational age	Christensen (6)	Clinical Trial	2010	Pound	-	£23'807	-	-	-	-	-

3.3. Quality Control

The CHEC checklist was used to assess the quality of the studies. Based on this checklist, as shown in Table 3, the scores were 18 for three studies, 17 for one study, 16 for two studies, 15 for two studies, 13 for one study, and 12 for two studies.

Table 3. Quality Analysis of Selected Studies

Q	1	2	3	4	5	6	7	8	9	10	11
1	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No
5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	No	No	Yes	Yes	Yes	No	Yes	No	No	No	No
15	yes	yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
16	No	No	Yes	Yes	Yes	No	Yes	No	No	No	No
17	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
19	No	No	No	Yes	No	No	No	Yes	Yes	No	No
20	No	No	No	No	No	No	No	Yes	Yes	No	No
Total	13	15	17	18	18	12	18	16	15	16	12

Abbreviations: No, number; Q, question; Y, Yes.

3.4. Data Analysis

The results of all studies confirmed the cost-effectiveness of GH in comparison to the non-treatment condition; however, the cost-effectiveness was different in various indications (namely Turner syndrome, idiopathic height shortage, GHD, Prader-Willi syndrome, small born babies for gestational age (SGA), chronic renal failure and SHOX).

Christensen et al. (2010) in a clinical trial study on SGA patients reported that the cost of per mg of medication was £21.39. Takeda et al. (10) reported that the cost of each mg of the growth hormone for SGA patients was $20.70. The US National Institutes of Health and Clinical Excellence (20) reports that the cost of per mg of medication in Turner syndrome, SGA, Prader Wiley, growth hormone deficiency, short stature without cause is 18 pounds. Christensen et al. (2010) in a cohort study on SGA patients and growth hormone deficiency reported that the cost of per mg of medicine was 234 SEK.

Christensen et al. (16) in a clinical trial on SGA patients and growth hormone deficiency stated that the cost per cm of height gain was £4359. Takeda et al. in their study found that the cost of increasing height per cm for SGA patients was $2467. They have reported that the cost of increasing height per cm for GHD was 2256 in SGA, Turner Syndrome, Prader Wiley, and growth hormone deficiency. The cost also was $9540 for Turner Syndrome, $9001 for CRI, and $2467 for SGA Bryant et al. (8) claimed the obtained incremental cost per centimeter height increased about £6,000 for GHD.

Bryant et al. (8) also estimated the cost of treating growth hormone deficiency indication to be between £4310000 - £530000. Vitova et al. calculated a cost of about 15,000 CZK per QALY (ICER) in each patient for GHD. Christensen et al. (16) in a clinical trial reported a cost of £4,359 per cm. Christensen et al. obtained the cost of treating growth hormone deficiency indication was SEK 1,161,473 compared to lack of treatment, associated with additional quality years of 12/3 quality adjustment). According to Tasavon Gholamhoseini et al. (18), the share of medical treatment costs was 5,092,964,520 Rials, and the share of Kerman Provincial Health Insurance Organization costs was 71,175,443,448 Rials. Bolin et al. (11) found that the direct costs for patients treated by GH, compared to untreated patients, were 421851 SEK (€44 405) and 544344 SEK (€56 284) for males and females, respectively (1 dollar = 9.03 krona). Craig et al. (19) reported an average of 0.001 QALY for an average of £21.

Bryant et al. (8) reported the cost of £55,500 - £83,000 for the treatment of Prader Wiley. The Institute for Health and Clinical Excellence (20) reported a cost of £18 per mg of the medication. Takeda et al. (10) reported a treatment cost of $9001 for CRI. Twena et al. (15) announced the cost of treating SGA indication by somatropin (0.033 mg/kg/day), which was associated with additional quality years 12/12 quality adjustments (QALYs) at an incremental cost of SEK 1,161,473, compared to lack of treatment. The Institute for Health and Clinical Excellence also announced the cost of £18 per mg. In a cohort study, Christensen et al. (2010) estimated the cost of SEK 234 (SEK) per mg. In a clinical trial study, the findings indicated the cost of £21.39 per mg of the medicine. Bryant et al. (8)£ estimated the effect of GH treatment for GHD on height increase in children treated with growth hormone up to 11 cm, compared to children who received no growth hormone. They stated that the height gained for GHD ranged from 11 to 8 cm. Vitova and Tichopad (14) examined the outcome of growth hormone treatment in a hypothetical group of 10,000 boys with 95017 incremental QALY and 1.6 CZK additional costs over a lifetime horizon. For a hypothetical group of 10,000 girls, 11504 incremental QALY and 351 CZK additional costs were announced. Christensen et al. reported that the patients' height was 108.53 (13.19) at the beginning of the study and reached 167.87 (6.81) at the end of the study. HSDS was -3.12 (0.70) at the beginning of the study and reached (0.65) -1.14 at the end of the study. They also reported a height increase of 108.53 cm at the beginning of the study and 167.87 at the end of the study. Tasavon Gholamhoseini et al. (18) reported that the height gain in patients with growth hormone deficiency was 174.4 and it was 90 for the patients without treatment. Bolin et al. (11) studies the effects of the treatment and found out that increasing height occurs in the first year, and that the change in QoL-AGDHA in the following years is caused by aging. The risk of mortality is assumed to vary based on age and gender; however, in the QoL-AGDHA government, there was no difference between the groups in this regard. The National Institute for Health and Clinical Excellence (20) reported an average height of 27.45 cm as an indication of growth hormone deficiency. Takeda et al. (10) reported growth hormone deficiency indication to be 6.7 cm in younger children after two and a half years.

Bryant et al. (8) found a height increase of 11 cm for PWS-treated children, compared to children who did not receive growth hormone. The National Institute of Health and Clinical Excellence (20) achieved a mean height of 3.65 cm for CRI. Takeda et al. (10) reported that, with regard to Prader Wiley syndrome, infants receiving RhGH for one year were significantly taller (6.2 cm) than the untreated ones. Bryant et al. (8) reported a 5-cm increase in Turner syndrome patients. The National Institute of Health and Clinical Excellence obtained a mean height of 7.95 cm in Turner syndromes. Takeda et al. reported significantly higher levels of HtSDS in the treated girls. Bryant et al. (8) reported a height increase of 3 - 9 cm in CRF patients. The mean height for CRI patients was 3.65 cm, according to the National Institute of Health and Clinical Excellence. Bryant et al. (8)· reported the height of ISS patients treated with growth hormone between 2 - 7 cm. Tasavon Gholamhoseini et al. (18) in their study on patients having short stature without cause found that the height gain was 174.4 for growth hormone treatment and 90 for the absence of treatment. The National Institute

for Health and Clinical Excellence (20) reported a mean height of 27.45 cm in short stature without cause.

Twena et al. (15) reported the consequences of using growth hormone in SGA patients, stating that somatropin (0.033 mg/kg/day) during one patient's life was associated with additional quality years 12/12 (QALYs) and the incremental cost of SEK 1,161,473, compared to the lack of treatment. Somatropin (Norditropin®) was associated with an increased cost for SEK 372,861 per QALY, in comparison to the lack of treatment. The possible sensitivity analysis with a variety of parameters showed that somatropin (Norditropin®) was likely to be cost-effective and was SEK 600,000 per QALY based on a willingness to pay. Christensen et al. also concluded that increased height in SGA patients was 108.53 (13.19) at the beginning of the study and reached 167.87 (6.81) at the end of the study. HSDS was -3.12 (0.70) at the beginning of the study and reached (0.65) -1.14 at the end of the study. Christensen et al. reported a height of 108.53 cm at the beginning of the study and 167.87 at the end of the study. The National Institute of Health and Clinical Excellence (20) reported a mean height of 5.67 cm for patients. Takeda et al. (10) reported an increase in the height of 3-year-old children without growth by about 4 cm.

Takeda et al. (10) in a study on the effects of growth hormone use on SHOX-D reported that children were about 6 cm taller than the control group after two years of treatment, and HtSDS was statistically significant in treated children. During the one-year study, they grew 2.7 cm in height and had higher standard deviation scores (-2.3 vs. -2.8), compared to the untreated children. Bryant et al. (8) estimated the incremental cost per cm of height gain for GHD to be about £6,000. Vitova et al. (14) in a sensitivity analysis showed that ICER did not exceed the considered uncertainty of CZK 50,000. In a clinical trial conducted in 2008, Christensen et al. found that the incremental efficacy cost of somatropin, compared to the lack of treatment with GH, was £70263 with QALY of 2.95. The obtained incremental cost-effectiveness was £23807, which was below the UK efficiency threshold of 30,000. One-way sensitivity analysis indicated that the results were sensitive to the changes in the discount rate of the results, the height of the children at the beginning of the study, and the useful values. Moreover, the probabilistic analysis showed that somatropin was cost-effective in 68.74% of the simulations, given the threshold of willingness to pay £30,000 per QALY.

Christensen et al. estimated the incremental cost of using growth hormone for GHD and stated that treatment with somatropin resulted in an additional 3.25 QALYs with an incremental cost of SEK 391.291. This is equivalent to an incremental cost per QALY of SEK 240,831 and SEK 120,494 for the SGA and GHD, which were below the future threshold cost of SEK 500,000 - 600,000/QALY, respectively. Samotropin is a cost-effective treatment strategy in Sweden for children with GHD. Tasavon Gholamhoseini et al. (18) noted that the treatment of short stature children using the growth hormone was cost effective. The incremental cost-effectiveness ratios based on Kali's criterion were 743,133 Rials and 9,846,567 Rials from the perspective of the patient and the Health Insurance Organization, respectively. Bolin et al. (11) reported an increase in the GH cost in GHD patients, SEK 410974 (€43 260) in men and SEK500263 (€52 659) in women. The mean annual life expectancy rates were 3.4 (male) and 2.7 (female), and the mean QALYs were 3.0 (men) and 2.8 (women). Regardless of the indirect costs, the total ICER was SEK 11390 (EUR 14637) and EUR 205850 (EUR 21 668), respectively. The key determinants of outcomes were improved quality of life, increased survival, and GH costs. GH (genotropin) treatment in adult patients with GHD is cost-effective, in comparison to unofficial Swedish thresholds, whereas the incremental cost in QALY is estimated between 100,000 (€10 526) and 500,000 SEK (€633 523). Craig et al. (19) found an incremental cost-effectiveness ratio in growth hormone deficiency patients to be £1144 per QALY. According to them, ICER did not exceed £8,000under no scenario. Takeda et al. (10) reported the cots from £20,000 to £30,000 per QALY in growth hormone deficient patients, according to the threshold of willingness to pay. The incremental cost-effectiveness for these patients was £20,673. Takeda et al. (10) reported that an annual incremental cost based on healthy living (QALY) estimated from RhGH compared to lack of treatment was £23,196 versus, £39,460. The probability of treatment for this disease was 95%, and the treatment cost was £30,000.

In a cohort study on the growth hormone deficient patients, Christensen et al. (2010) reported that the incremental costs per QALY was 240,831 SEK and 120,494 SEK for SGA and GHD, respectively, which were below the cost-effective threshold of 500,000 - 600,000 SEK/QALY. Samotropin is a cost-effective treatment strategy in Sweden for children with GHD. The National Institute for Health and Clinical Excellence (ICER) (20) announced the incremental cost-effectiveness for the disease to be £17,552. Bryant et al. (8) reported that the incremental cost per centimeter of height gain for Prader Willi Syndrome was £7030. Takeda et al. (10) showed that the cost-effectiveness ratio (ICER) in Prader-Willi Syndrome was between £55,000 and £135,000 per QALY (depending on the hypothesis), and the ICER was between £33,000 and £40 ,500 per QALY under other conditions. They found an incremental cost-effectiveness of £3,540 for patients with Prader Willi Syndrome and the incremental cost based on annual Healthy Living estimated in RhGH (QALY) compared to lack of treatment was £135,311 for PWS. The possible treatment for any of the conditions was estimated to be £30,000. The probability of treatment for these patients was 1%. Somatropin is also a cost-effective treatment strategy in Sweden for Prader Willi syndrome. The National Institute for Health and Clinical Excellence (20) reported the incremental cost-effectiveness (ICER (£/QALY) of £32,540 for PWS.

Twena et al. (15) stated about the cost-effectiveness of SGA patients that by assuming a willingness to pay SEK 600,000 per QALY, somatropin (Norditropin®) is a cost-effective cost recovery strategy for short-stature children (SGA) in Sweden providing significant incremental health benefits with an additional cost. Christensen et al. reported the cost-effectiveness of somatropin treatment in SGA patients with an increase of 3.29 QALY, the incremental cost was SEK 792,489 (SEK) compared to lack of treatment. This is equivalent to the incremental costs per QALY of SEK 240,831 and SEK 120,494 for SGA and GHD, respectively, which are below the future threshold cost of 500,000 - 600,000 SEK/QALY. Takeda et al. (10) reported an SGA incremental cost-effectiveness ratio of £18,167. The incremental cost was $079 on the basis of the annual Healthy Living QALY estimated by RhGH, compared to the lack of treatment. The probability of treatment under each of the conditions at a cost of £30,000 was 38% for the SGA.

Bryant et al. (8) reported an incremental cost per centimeter of height gain for Turner Syndrome between £16,000 and £17,000,000. They also reported 19% treatment probability for any condition that cost £30,000 for TS. National Institute for Health and Clinical Excellence reported an incremental cost-effectiveness of £29,757 (ICER (£/QALY) for Turner Syndrome.

Takeda et al. (10) reported the incremental cost of $2400 to $7400 per cm of height gain for CRF patients and the incremental cost-effectiveness of £15,962 for CRI. The National Institute for Health and Clinical Excellence (20) reported the incremental cost-effectiveness of £15,962 (£/QALY) for CRI.

Takeda et al. (10) announced the incremental costs of £40,531 based on the annual healthy living (QALY) estimated by RhGH, compared to lack of treatment for SHOX-D, and stated the treatment probability of 15% under any condition at the cost of £30,000 for SHOX-D.

Bryant et al. (8) reported the incremental cost of $2700 - $500 of per cm of height gain for ISS. Takeda et al. (10) found the cost-effectiveness of £20,673 for GHD continued treatment. The National Institute for Health and Clinical Excellence (20) reported the incremental cost-effectiveness of £20,673 (£/QALY) for GHD continued.

The incremental cost was £33 on the basis of the annual healthy living QALY estimated by RhGH, compared to the lack of treatment (£23,196) for CRI. They expressed 38% treatment probability under any condition costing £30,000 for CRI. The National Institute for Health and Clinical Excellence reported the incremental cost-effectiveness ratio of £15,962 for CRI.

4. Discussion

This study aimed to evaluate the cost-effectiveness of GH drug and its consumption, and a systematic review of the incremental cost-effectiveness ratio (ICER) was considered as the measurement criterion.

Studies on indications (Turner syndrome, idiopathic short stature, growth hormone deficiency, Prader Willi syndrome, small for gestational age (SGA), chronic renal failure (CRF), Failure and short stature homeobox-containing gene (SHOX-D) deficiency) showed that the use of growth hormone is cost-effective, compared to the lack of treatment, for all the aforementioned conditions (8, 10, 19). The lowest cost per kali was related to Prader Willi and the highest cost per kali was for growth hormone deficiency. The other indications based on cost-effectiveness were familial short stature, infants younger than gestational age, chronic renal failure, Turner syndrome, and SHOX-D, respectively.

Ivko et al. (2010) in their study showed that the use of growth hormone for patients with Turner syndrome was cost effective, and its incremental cost effectiveness ratio was £39460.

Moreover, Bryant et al. (8) and the US NICE (2010) found that using growth hormone was cost-effective for patients with Turner syndrome, and its cost effectiveness ratios for each QALY were £29,757 and £39,460, respectively (8, 10, 19).

According to some review studies on patients with idiopathic short stature (e.g., the US NICE (2010), Takeda et al. (10), and Bryant et al. (8)), the use of growth hormone for these patients was cost-effective and its incremental cost-effectiveness ratios (ICER) for each QALY were obtained £20763, £23196, and £20 - £30,000, respectively (8, 19).

Vitova et al. (14) claimed that using growth hormone for patients with growth hormone deficiency was cost-effective, and the incremental cost-effectiveness ratio was 157,000 kronor per QALY. Moreover, in a study conducted by Tasavon Gholamhoseini et al. (18), the incremental cost-effectiveness for each QALY was 9846567 Rials.

Bolin et al. (11), Craig et al. (19), Bryant et al. (8), US NICE (2010) and Christensen et al. (20) used growth hormone for patients with growth hormone deficiency, and the incremental cost effectiveness ratios for each QALY were €15,975 to 20241, £1144, £20 - £30,000, £17552, and 120494 Czech koruna, respectively (6, 11, 14, 17).

A study by Takeda et al. (10) showed that the use of growth hormone in patients with Prader Willi syndrome was cost- effective and its incremental cost-effectiveness for each QALY was, £135315. In a study by Bryant et al. (8), they also found an incremental cost-effectiveness ratio of $55,000 to $135,000 per QALY. The US NICE (2010) also found an incremental cost-effectiveness ratio of £ 32,540 per QALY (8, 10, 19).

In a study by Christensen et al. (2010), they found that the use of growth hormone in SGA patients was cost-effective, and its incremental cost-effectiveness rate per QALY was £ 23807. Moreover, Takeda et al. (10) found that the use of growth hormone for patients with SGA was cost-effective, and its incremental cost-effectiveness was £33079 per QALY. Moreover, some other studies (e.g., the US NICE (2010), Christensen et al. (2008), Twena et al. (15), and Bryant et al. (8)) concluded that the use of growth hormone was cost-effective for patients with SGA, and its

incremental cost-effectiveness for each QALY was £18167, £26794 Tristan da Conha Pounds, 372361 Swedish krona, and 33 to £40500, respectively (8, 16).

In a study by Takeda et al. (10), the researchers noted that the use of growth hormone for patients with chronic renal disease (CRF) was cost-effective, and its incremental cost-effectiveness was £39272 per QALY. Furthermore, in two studies by the US NICE (2010) and Bryant et al. (8), they found that the use of growth hormone for patients with chronic renal failure was cost effective, and its cost-effectiveness rate for each QALY was £15962 and £33 to 40500, respectively (8, 10, 19).

Takeda et al. (10) in 2010 claimed that using GH was cost-effective for patients with SHOX-D. A study by Bryant et al. (8) in 2002 also revealed that the use of growth hormone was cost-effective for SHOX-D patients. In these two studies, incremental cost-effectiveness for each QALY was estimated to be £40531 and £33 to £40500, respectively.

5. Conclusions

According to the concerned studies, the GH is a cost-effective intervention; hence, it is recommended for short stature patients and those who have the required cost-effectiveness. GH is cost-effective for children with GHD, Prader-Willi syndrome, short stature with no cause, and Turner syndrome; thus, it can be considered by policy makers in their health plans. Regarding the gap in this field, it future studies are suggested to examine the quality of life in short stature patients as well as the cost of their treatment.

Acknowledgments

This study was extracted from a M.A. thesis in Health Technology Assessment, supported by Yazd University of Medical Sciences.

Conflict of Interests: The authors declare that there is no conflict of interest in this study.

References

1. Assar SSH, Riahi K, Kheradmand K. Frequency of growth hormone deficiency in short stature children. J Isfahan Med Sch. 2010;28:104.
2. Germanyuk T, Kryvoviaz O, Toziuk O, Balicka O, Ivko T, Polyshchuk Y, et al. Dwarfism: Accessibility of somatropin therapy for patients with growth hormone deficiency and impact of its cost on the state budget in Ukraine. Asia J Pharm. 2017;11(4):794-7.
3. Maeda E, Higashi T, Hasegawa T, Yokoya S, Mochizuki T, Ishii T, et al. Effects of financial support on treatment of adolescents with growth hormone deficiency: A retrospective study in Japan. BMC Health Serv Res. 2016;16(1):602.
4. Howard SR, Butler GE. An analysis of the clinical and cost effectiveness of growth hormone replacement therapy before and during puberty: Should we increase the dose? Horm Res Paediatr. 2013;79(2):75-82.
5. Saz-Parkinson Z, Granados Alonso MDS, Amate JM. Study of adherence to recombinant growth hormone treatment of children with a GH deficiency: Contributions to treatment control and economic impact. Madrid: Instituto de Salud Carlos III; 2013.
6. Christensen T, Buckland A, Bentley A, Djurhuus C, Baker-Searle R. Cost-effectiveness of somatropin for the treatment of short children born small for gestational age. Clin Ther. 2010;32(6):1068-82.
7. Valentim J, Passos V, Mataveli F, Calabro A. Cost-effectiveness analysis of somatostatin analogues in the treatment of acromegaly in Brazil. Arq Bras Endocrinol Metabol. 2008;52(9):1452-60.
8. Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, et al. Clinical effectiveness and cost-effectiveness of growth hormone in children: A systematic review and economic evaluation. Health Technol Assess. 2002;6(18):1-168.
9. Yokoya S, Tanaka T, Itabashi K, Osada H, Hirai H, Seino Y. Efficacy and safety of growth hormone treatment in Japanese children with small-for-gestational-age short stature in accordance with Japanese guidelines. Clin Pediatr Endocrinol. 2018;27(4):225-34.
10. Takeda A, Cooper K, Bird A, Baxter L, Frampton GK, Gospodarevskaya E, et al. Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. Health Technol Assess. 2010;14(42):1-209, iii-iv.
11. Bolin K, Jonsson B, Koltowska-Haggstrom M, Prutz C, Sandin R, editors. The cost-effectiveness of growth hormone (GH) treatment (Genotropin [reg]) in adult patients with growth hormone deficiency (GHD). 11th European Congress of Endocrinology; 2009; Turkey BioScientifica.
12. Joshi AV, Munro V, Russell MW. Cost-utility of somatropin (rDNA origin) in the treatment of growth hormone deficiency in children. Curr Med Res Opin. 2006;22(2):351-7.
13. Wijnen B, Van Mastrigt G, Redekop WK, Majoie H, De Kinderen R, Evers S. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: Data extraction, risk of bias, and transferability (part 3/3). Expert Rev Pharmacoecon Outcomes Res. 2016;16(6):723-32.
14. Vitova V, Tichopad A. Cost-effectiveness of somatropin administration with increased adherence due to monitoring compared to non-monitored administration in patients with growth hormone deficiency. Value Health. 2013;16(7):A622-3.
15. Twena N, Christensen T, Buckland A, Bentley A, Djurhuus CB. P-40 Economic evaluation of somatropin (Norditropin®) for the treatment of short children born SGA in Sweden. Growth Horm IGF Res. 2008;18:S39.
16. Christensen T, Buckland AG, Bentley A, Djuurhus C, Wing C. Pdb19 economic evaluation of somatropin (norditropin) for the treatment of short children born small for gestational age (Sga). Value in Health. 2008;11(3):A223.
17. Christensen T, Fidler C, Bentley A, Djurhuus C. The cost-effectiveness of somatropin treatment for short children born small for gestational age (SGA) and children with growth hormone deficiency (GHD) in Sweden. J Med Econ. 2010;13(1):168-78.
18. Tasavon Gholamhoseini M, Barouni M, Afsharzadeh N, Jafari Sirizi M. Cost-effectiveness of growth hormone (somatropin) for the treatment of children with short stature. J Payavard Salamat. 2018;12(4):286-95.
19. Craig D, Fayter D, Stirk L, Crott R. Growth monitoring for short stature: update of a systematic review and economic model. Health Technol Assess. 2011;15(11):iii-iv, 1-64.
20. National Institute for Health and Clinical Excellenc. Human growth hormone in children (review of NICE technology appraisal guidance 42). National Institute for Health and Clinical Excellence; 2009.