Patient Related Outcome Measures

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ORIGINAL RESEARCH

Utilities Associated with the Treatment of Growth Hormone Deficiency (GHD): A Time Trade-off (TTO) Study in the UK and Canada

Susan Kirsch[1], Gary Butler[2], Lasse de Fries Jensen[3], Anna Okkels[4], Cecilie Yssing[4], Jonas Håkan-Bloch[3]

[1]Department of Pediatric Endocrinology, Hospital for Sick Children, Toronto and Oak Valley Health Hospital, Markham, Ontario, Canada; [2]Department of Paediatric Endocrinology, University College London Hospitals, and UCL Great Ormond Street Institute of Child Health, London, UK; [3]Novo Nordisk, Søborg, 2860, Denmark; [4]EY Godkendt Revisionspartnerselskab, Frederiksberg, 2000, Denmark

Correspondence: Lasse de Fries Jensen, Novo Nordisk, Vandtårnsvej 108-110, Søborg, 2860, Denmark, Tel +45 34482020, Email LDFJ@novonordisk.com

Purpose: Growth hormone deficiency (GHD) causes decreased growth rate in children, resulting in short stature in childhood and adulthood. Daily subcutaneous injections with growth hormone (GH) have been standard treatment. Newer weekly GH formulations now exist. This study estimates utilities associated with GHD treatment for both people with the disease and caregivers by employing time trade-off (TTO) methodology.

Methods: Three online surveys were conducted amongst the general population in the UK and Canada. Based on a pilot, data collection was conducted in two surveys only (Survey A and Survey B). In Survey A, adults aged ≥18 years evaluated health states as if they were receiving injections themselves. In Survey B, adults with a child <15 years evaluated health states as if they were administering injections to a child. The surveys assessed device complexity, injection frequency, injection pain, needle visibility and storage possibilities.

Results: 2026 and 2028 respondents completed Survey A and Survey B, respectively. Of these, 1782 respondents and 1678 respondents were valid for inclusion. Avoiding weekly injection pain was associated with a significant utility gain of 0.030 (95% CI 0.026–0.035, p<0.001) in Survey A and 0.044 (95% CI 0.038–0.051, p<0.001) in Survey B. Additionally, less complex injection devices and lower injection frequencies had a significant impact in both Survey A (0.020, 95% CI 0.016–0.025, p<0.001; 0.009, 95% CI 0.005–0.014, p<0.001) and Survey B (0.008, 95% CI 0.002–0.014, p=0.006; 0.009, 95% CI 0.003–0.014, p=0.003).

Conclusion: Several aspects are associated with a significant impact on utilities for people with GHD and potential caregivers. Treatment options without injection pain, a time-consuming and complex injection process and daily injections are expected to result in higher health-related quality of life. These results may inform future economic evaluations and treatment choices.

Keywords: caregiver, children, health-related quality of life, survey

Introduction

Growth hormone deficiency (GHD) is a rare condition caused by an insufficient production of growth hormone (GH) in the pituitary gland.[1] In studies conducted in the US and Europe, the prevalence of childhood GHD has been reported to be between 1.8 and 2.9 per 10,000.[2–4] Additionally, a Danish study reported the incidence of childhood-onset GHD to be 1.7 for females and 3.6 for males per 100,000.[5]

GHD is one of the most important endocrine-related causes of short stature.[6] In childhood, GHD is associated with symptoms such as absence of strength, lower energy levels, unproductive sleep and poor muscle development as well as reduced appetite.[7] In addition to the physical symptoms, GHD has an impact on multiple aspects of daily life, including the child's social and emotional well-being.[7] Children with GHD also face a greater comorbid burden compared with demographically matched controls.[8] Adults with GHD have increased cardiovascular mortality, lower muscle tone,

Received: 3 September 2024
Accepted: 30 December 2024
Published: 10 January 2025

increased central abnormal adiposity, hyperlipidaemia, low bone mineral density, psychological effects and poorer health-related quality of life (HRQoL) compared with the general population.[9,10]

GH therapies have been given as daily subcutaneous injections with GH since the 1980s. However, newer GH formulations given as weekly subcutaneous injections have been available in the US since the 2020s.[10–15] Despite the recognised benefits of GH therapy, several aspects of GHD treatment have shown to be burdensome.[16–18] Factors such as storage, injection device, injection frequency, injection pain and preparation are some of the aspects with a high impact.[17] Previous findings indicate that 43% of people with GHD miss injections if the medication must be stored in the fridge, whilst the figure is 24% if the storage requirements are more flexible.[19] Furthermore, treatments associated with complex administration could lead to non-adherence, and relatively easy-to-use treatment options are more desirable amongst people living with GHD.[18,20] The treatment burden of GHD is also substantial for potential caregivers.[21–23] For instance, 62% of parents worry about treatment administration when giving GH therapy to their child, 38% worry about causing pain to their child and 15% are frustrated with the injection administration.[16]

To measure the impact on HRQoL amongst people living with a specific disease and to inform economic evaluations, several health technology assessment (HTA) agencies require health state utility values (HSUVs). A number of HTA agencies also recommend inclusion of HSUVs for potential caregivers in relevant cases[24] such as GHD due to the disease occurrence in childhood. Generic preference-based measures, including, eg EuroQol-5 Dimension (EQ-5D) and Short-form 6-dimension (SF-6D), are often the preferred method when generating HSUVs.[24] However, there are situations where these are insufficient, eg in evaluations of rare diseases, where patient populations are small. In these situations, vignettes are a preferred tool. In addition to being an alternative for generic measures, vignettes offer the opportunity for making more condition-specific evaluations and measuring even small differences in HSUVs related to a specific disease or treatment.[24,25] Time trade-off (TTO) methodology is an accepted preference elicitation technique when estimating HSUVs through the evaluation of vignettes. The TTO methodology is acknowledged by several HTA agencies, including the National Institute for Health and Care Excellence (NICE) in the UK and the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada.[24–27]

Whilst the methodology for evaluating health in an adult population is well established, robust guidelines for the most appropriate approach for children and adolescents have not yet been developed.[28] Earlier research has identified multiple challenges when valuing health amongst children, even though several methods have been applied and discussed.[28–30] One option is to ask a population of children and adolescents, since they can relate to how the condition could impact their lives. However, several contrary arguments emphasise that asking children and adolescents is inadequate, perhaps because they might not be able to understand the TTO questions.[31] Another approach could be to ask adults to imagine being a child. However, earlier studies have found that the willingness to trade life years is strongly impacted by the perspective used in the survey as well as how the perspective is described.[29,32] Additionally, imagining being a child is difficult, which results in variations in what is imagined by the respondents.[29] These issues when valuing health amongst children make it challenging to generate HSUVs related to GHD treatment, and different approaches can be applied.

The aim of this study was to estimate utility gains or disutilities associated with GHD treatment for both people living with the disease, including children, and potential caregivers to inform future economic evaluations. This was investigated by evaluating several treatment aspects using TTO surveys in the UK and Canada.

Materials and Methods

The TTO Methodology

When using the TTO methodology, respondents are asked to choose between two health states (HSs): An impaired HS for an amount of life, t, and an HS in full health but for a shorter amount of life, x. By choosing the preferred HS, respondents "trade" a part of their life in order to live in full health instead of living in an impaired HS.

To identify the point where the two presented HSs are equally attractive to the respondents (point of indifference), they are repeatedly asked to choose between the impaired HS versus full health. Respondents who choose the impaired health state will be asked to trade a smaller number of life years in the next question, while respondents who choose to trade life years to live in full health are asked to trade a larger number of life years in the next question. Thus, for each

trade, the number of years lived in full health, x, is varied until the point of indifference is identified, x*. An HSUV between 0 and 1 is calculated based on this point of indifference. The HSUV is calculated as x*/t (0=death, 1=full health).[33,34]

Study Population

When using the TTO methodology to elicit HSUVs for health economic evaluations, it is generally recommended by HTA agencies to use HSUVs elicited from the general population, ie not the population living with the condition.[24–27] This recommendation is often based on the idea of social decision-making, which reflects that healthcare decision makers are acting on behalf of the general population. Therefore, the population in this study consisted of the adult general population in the UK and Canada.

To manage the challenges when valuing health amongst children, two surveys were developed based on discussions in the literature on the best approaches for measuring child health.[28,31] In the first survey, HSUVs of the adult general population were used as a proxy for children. In the second survey, utility values of the adult general population were elicited by asking the respondents to imagine that they were diagnosed with GHD as a child. To value health amongst caregivers, a third survey was developed in which an adult general population was asked to imagine themselves being a caregiver of a child living with GHD. For all three surveys, the inclusion criteria were (1) consent to participate and (2) at least age 18 years. As recommended by Powell et al and to increase relatability, only respondents with at least one child under the age of 15 were included in the third survey.[29]

Respondents who had previously agreed to participate in internet-based surveys were recruited through existing Email panels. Respondents were rewarded (cash) points equivalent to EUR/CAD 1–2 for participation. The surveys were answered anonymously, and no sensitive information was collected or revealed. Additionally, the surveys were conducted according to the codes of conduct of the European Society for Opinion and Market Research (ESOMAR) and the Canadian Research Insights Council (CRIC) and followed the applicable guidelines. Since this study was not a clinical trial, it did not include patients, it did not gather biological or human samples or identifiable personal information, it was not carried out or funded by Health Canada or Public Health Agency of Canada, and it was not taking place in a National Health Service (NHS) setting; ethical review board approval was not required in Canada and the UK (as described by NHS Health Research Authority in the UK and in the Canadian TCPS2 2022).

Description of Disease and Definition of Health States

In the beginning of each of the three surveys, respondents were presented with an introduction to GHD and a description of the perspective (Figure 1). In the first survey, respondents were asked to imagine having a hormone deficiency disease, and in the second survey, respondents were asked to imagine that they were diagnosed with GHD at the age of 5. In the third survey, respondents were asked to imagine having a 5-year-old child diagnosed with GHD.

Based on input from clinical experts and findings from a previous qualitative study of the treatment burden for children living with GHD and their caregivers,[16] the following five GHD treatment aspects were evaluated in each of the three surveys: injection frequency, device complexity, needle visibility, injection pain and storage possibilities. To make the results as accurate as possible, the treatment aspects were defined using product information from existing treatment options and a definition of injection pain from a previous Phase 3 clinical trial.[35] Table 1 presents the final definition of the five treatment aspects, and Figure S1 provides an example of how the treatment aspects were described to the respondents.

To elicit the utility gain or disutility associated with each of the five GHD treatment aspects, eight HSs were designed and included in each of the three surveys. Table 2 presents an overview of how the GHD treatment aspects were described in the eight HSs.

Survey Design

The surveys were programmed in a commercial survey software package (SurveyXact). To make the trade-offs as realistic as possible, the time horizons applied in the surveys varied depending on each respondent's individual life

Short description before the exercise

Survey 1: The general population evaluating health states as if they took injections themselves

Now we would like you to imagine having a hormone deficiency disease. You can get treatment that keeps the hormone deficiency disease under control without side effects.

If left untreated, the deficiency will reduce both your muscle mass as well as bone mass and increase your body fat mass. The symptoms interfere with your everyday life and impact your quality of life both physically and mentally.

The treatment needed to keep the disease under control will interfere with your life.

Survey 2: The general population evaluating health states as if they were a child with GHD

Now we would like you to imagine that you were diagnosed with growth hormone deficiency at the age of 5.

If left untreated, the deficiency would cause a slower growth in your height, meaning that you would not grow to the height you have today. Furthermore, it would reduce your muscle mass and bone mass, increase the level of fat around your stomach, cause impaired hair growth and delayed puberty. The symptoms would interfere with your everyday life and impact your physical, social and emotional well-being. For instance, you might experience bullying or being treated differently than peers by adults. Additionally, you might experience feelings such as poor self-confidence, embarrassment or frustration because of the condition.

Appropriate medical treatment would fully cure the deficiency. However, the treatment would interfere with your life.

Survey 3: The general population evaluating health states as if they gave injections to a child with GHD

Now we would like you to imagine having a child that is 5 years old and has been diagnosed with growth hormone deficiency.

If left untreated, the deficiency slows your child's growth in height and reduces muscle mass. Furthermore, your child may have an increased level of fat around the stomach, impaired hair growth and delayed puberty.

The symptoms interfere with your child's everyday life and impact his/hers social and emotional well-being. For instance, your child might experience bullying or being treated differently than peers by adults. Additionally, your child might experience feelings such as poor self-confidence, embarrassment or frustration because of the condition.

Appropriate medical treatment can fully cure the deficiency. However, the treatment will interfere with your life.

Figure 1 Description of GHD applied in the three surveys.

expectancy, calculated using the respondent's age and gender as well as the most recent lifespan tables from the World Health Organization.[36]

The point of indifference was identified by presenting each trade-off between an impaired HS and a full health HS four to six times but with different lifetimes for full health (always shorter than the impaired HS). For each choice made by the respondents, the difference in the lifetime for the full health option was narrowed until the point of indifference was identified. This procedure followed a standard bisection methodology, using a utility of 0.6 as a starting point to reduce the utility value to an interval of 0.025.

When using an online survey to estimate HSUVs, it is crucial that the respondents understand and accept the premises of the research and that they continue to be motivated to provide considered answers throughout the survey. Thus, to increase the validity of results, the following three features were built into the survey design. First, to familiarise the respondents with the

Table 1 Overview of Evaluated Aspects in the Treatment of GHD

Aspect	Opportunities	Description
Injection frequency	Daily	Once a day just before bedtime.
	Weekly	Once a week on the same day each week.
Device complexity	Complex	An injection process which takes 5–10 minutes and consists of nine steps.
	Less complex	An injection process which takes approximately 1 minute and consists of four steps.
Needle visibility	Visible	Always visible.
	Invisible	Invisible at the time of injection.
Injection pain	No injection pain	An injection process which does not cause any pain during or after the injection.
	Injection pain	An injection process which causes pain that corresponds to a score of 4 on a scale from 0 to 5, where 0 is "no hurt" and 5 is "hurts worse". The pain is transient and does not limit activities. No medical intervention/ therapy is required.
Storage	Fridge	Must always be stored in the fridge.
	RT	Can always be stored at room temperature.
	RT <72 hours	Must be stored in the fridge but can be kept at room temperature for up to 72 hours, if necessary.

Abbreviation: RT, room temperature.

Table 2 Overview of Health States Evaluated in the Three Surveys

Health State	1	2	3	4	5	6	7	8
Injection frequency	Weekly	Weekly	Weekly	Daily	Weekly	Daily	Weekly	Weekly
Device complexity	Less complex	Less complex	Less complex	Less complex	Complex	Less complex	Complex	Less complex
Needle visibility	Visible	Visible	Invisible	Visible	Invisible	Visible	Invisible	Visible
Injection pain	No	Yes	No	No	No	No	No	No
Storage	Fridge	Fridge	Fridge	Fridge	Fridge	RT	RT	RT <72 h

Abbreviation: RT, room temperature.

TTO concept and to test their understanding of the methodology, a "warmup" exercise was implemented as the first HS in all surveys. The exercise included a TTO test question with a choice of (1) full health and a long remaining lifetime or (2) impaired health and a reduced lifetime. Respondents who chose the second option were excluded from the TTO analysis. Second, respondents who chose not to trade any lifetime or who chose to trade a very large proportion of their remaining lifespan were screened carefully before inclusion in TTO analyses. Respondents were excluded from the analysis of the specific HS if they reported that their choice was due to ethical or religious beliefs or if they stated that they did not understand the question. Respondents who reported that their choice was due to a manageable HS or a desire to live as long as possible, eg due to obligations in their life, were kept in the further analysis. Finally, to avoid fatigue and thereby potentially less-considered trade-offs, respondents only received trade-off scenarios for five of the eight HSs. The order in which HSs were presented to respondents was randomised to ensure that the results for each HS were not affected by the order.

The functionality of the three surveys was tested in a pilot study in the UK. In the second survey, an unusually high dropout rate of respondents was observed (28% vs 8% in the first survey and 4% in the third survey) due to their not understanding the test question. Based on these results as well as recommendations from the literature, it was decided to elicit HSUVs for people with GHD using only the first survey. Thus, the main data collection was completed for the first and third surveys only (hereafter, Survey A and Survey B). Survey A was conducted to elicit utilities for people with GHD, including children, and Survey B was conducted to elicit utilities for caregivers of children with GHD. The main data collection was conducted, in both the UK and Canada, from October to December 2022.

Statistical Analysis

The aim was to estimate the average utility gain or disutility associated with different aspects of GHD treatment (Table 1). Based on the respondents' trade-offs, an HSUV was calculated for each of the eight HSs. The value represents

the midpoint of the chosen range of indifference. Using these HSUVs for all respondents, an average HSUV for each HS was estimated. Thereafter, utility gains/disutilities were calculated as the difference between the average HSUVs of two HSs. For instance, the only difference between HS 1 and HS 2 was the presence of injection pain (Table 2). Thus, by calculating the difference between the average HSUV elicited for the two separate HSs, a utility gain/disutility for avoiding injection pain could be estimated.

To mitigate the risk of including people who do not provide considered responses, the 5% most extreme values were excluded (2.5% at each end). This ensures better confidence in the results and makes the analyses less sensitive to outliers. Non-parametric bootstrapping with 10,000 iterations was used to simulate standard errors and confidence intervals (CIs) and to test differences between the parameters.

Statistical analyses were conducted using SAS version 9.4 statistical software.

Results

Study Population

In total, 2026 and 2028 respondents completed Survey A and Survey B, respectively. Of the respondents completing Survey A, 1025 were from the UK and 1001 were from Canada. Of the respondents completing Survey B, 1017 were from the UK and 1011 were from Canada. 244 and 350 respondents failed the TTO test question in Survey A and Survey B, respectively. Thus, 1782 and 1678 respondents were included in the further analyses (Figure 2).

Baseline characteristics are presented in Table 3. In Survey A, the study population was almost equally distributed by age group and gender. The majority were in full-time employment (45%) and had a bachelor's degree or higher (43%). In Survey B, the majority of the population was aged 30 to 50 years, most likely due to the inclusion criteria of having at least one child under the age of 15. Additionally, most respondents were female (55%), were in full-time employment (63%) and had a bachelor's degree or higher (53%).

TTO Results for Survey A

Table 4 presents utility gains/disutilities associated with the five aspects of GHD treatment when the population evaluated HSs as if they took injections themselves.

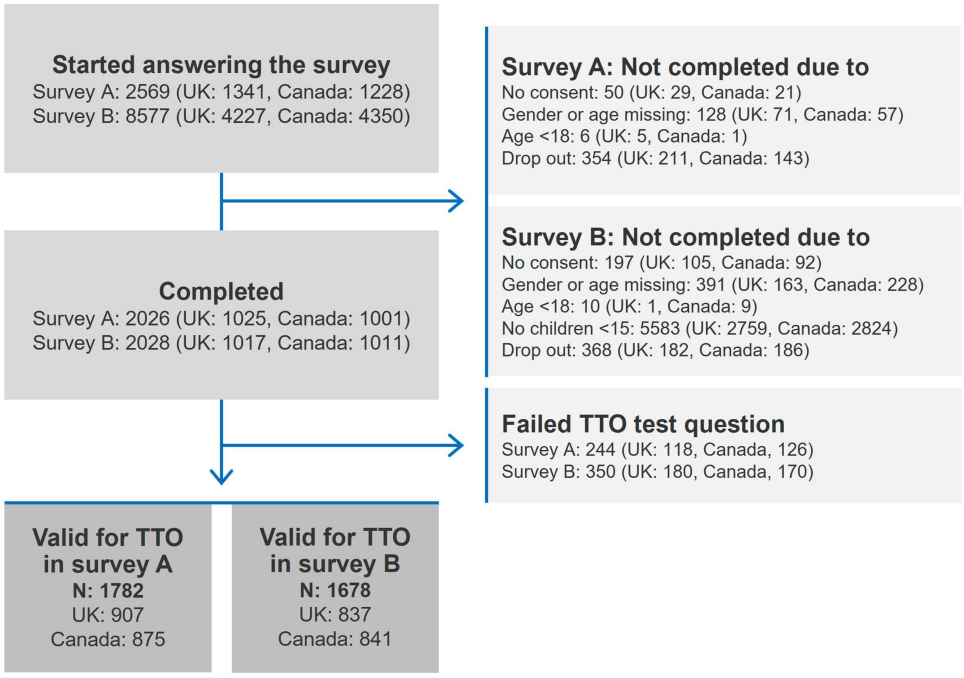

Figure 2 Respondent flowchart.

Table 3 Characteristics of Study Population

	Survey A			Survey B		
	Total	**UK**	**Canada**	**Total**	**UK**	**Canada**
Total, n	2026	1025	1001	2028	1017	1011
Age, n (%)						
<30 years	349 (17)	225 (22)	124 (12)	175 (9)	66 (6)	109 (11)
30–39 years	371 (18)	163 (16)	208 (21)	762 (38)	374 (37)	388 (38)
40–49 years	394 (19)	155 (15)	239 (24)	713 (35)	400 (39)	313 (31)
50–59 years	352 (17)	169 (16)	183 (18)	366 (18)	168 (17)	198 (20)
60–69 years	375 (19)	208 (20)	167 (17)	12 (1)	9 (1)	3 (<1)
70+ years	185 (9)	105 (10)	80 (8)	0 (0)	0 (0)	0 (0)
Gender, n (%)						
Female	1043 (51)	496 (48)	487 (49)	1119 (55)	478 (47)	431 (43)
Male	983 (49)	529 (52)	514 (51)	909 (45)	539 (53)	580 (57)
Employment status, n (%)						
Employed full-time	903 (45)	450 (44)	453 (45)	1286 (63)	633 (62)	653 (65)
Part-time (<32 hours week)	240 (12)	133 (13)	107 (11)	251 (12)	156 (15)	95 (9)
Self-employed	136 (7)	80 (8)	56 (6)	132 (7)	66 (6)	66 (7)
Not employed	156 (8)	54 (5)	102 (10)	194 (10)	93 (9)	101 (10)
Retired	405 (20)	214 (21)	191 (19)	19 (1)	6 (1)	13 (1)
Student	68 (3)	37 (4)	31 (3)	20 (1)	6 (1)	14 (1)
Permanent disability	80 (4)	39 (4)	41 (4)	47 (2)	21 (2)	26 (3)
Other	29 (1)	14 (1)	15 (2)	63 (3)	27 (3)	36 (4)
Missing	9 (<1)	4 (<1)	5 (1)	16 (1)	9 (1)	7 (1)
Educational level, n (%)						
Less than a high school	37 (2)	19 (2)	18 (2)	26 (1)	17 (2)	9 (1)
High school	443 (22)	243 (24)	200 (20)	299 (15)	179 (18)	120 (12)
Some college or associate degree	615 (30)	263 (26)	352 (35)	558 (28)	268 (26)	290 (29)
Bachelor's degree and higher	878 (43)	470 (46)	408 (41)	1082 (53)	516 (51)	566 (56)
Other	43 (2)	25 (2)	18 (2)	52 (3)	33 (3)	19 (2)
Missing	10 (<1)	5 (<1)	5 (1)	11 (1)	4 (<1)	7 (1)
Height in cm, mean (SD)	169.58 (11.93)	170.50 (11.29)	168.63 (12.48)	168.83 (13.31)	169.48 (12.79)	168.17 (13.79)

Table 4 Utility Gain or Disutility Associated with Different Aspects of GHD Treatment Elicited with Survey A

	Total			UK			Canada		
	N	**Utility**	**95% CI**	**N**	**Utility**	**95% CI**	**N**	**Utility**	**95% CI**
Avoid weekly pain[a]	1408	0.030*	0.026; 0.035	749	0.030*	0.025; 0.036	658	0.030*	0.023; 0.036
Avoid visible needle[b]	733	0.004	−0.0007; 0.008	391	0.004	−0.002; 0.009	341	0.004	−0.003; 0.011
Weekly instead of daily[c]	674	0.009*	0.005; 0.014	353	0.009*	0.004; 0.015	319	0.010*	0.003; 0.017
Less complex device[d]	741	0.020*	0.016; 0.025	397	0.019*	0.013; 0.026	341	0.023*	0.016; 0.030
RT instead of fridge[e]	1509	0.003	−0.002; 0.007	744	0.002	−0.004; 0.008	662	0.004	−0.003; 0.011
RT <72 hours instead of fridge[f]	679	−0.002	−0.007; 0.002	360	−0.004	−0.010; 0.002	317	−0.001	−0.007; 0.006

Notes: *P-value <0.05. [a]HS1 vs HS2, [b]HS1 vs HS3, [c]HS1 vs HS4, [d]HS3 vs HS5, [e]HS4 vs HS6 and HS5 vs HS7, [f]HS1 vs HS8.

Injection pain was considered the most important treatment aspect amongst the general population in both the UK and Canada. Avoiding weekly injection pain was associated with a significant utility gain of 0.030 in both countries (95% CI UK: 0.025–0.036, p<0.001, Canada: 0.023–0.036, p<0.001, total: 0.026–0.035, p<0.001).

A less complex injection device and a lower injection frequency were also preferred in both countries. In total, a less complex injection device was associated with a utility gain of 0.020 (95% CI 0.016–0.025, p<0.001) (UK: 0.019 (95% CI 0.013–0.026, p<0.001), Canada: 0.023 (95% CI 0.016–0.030, p<0.001)), and weekly instead of daily injections were

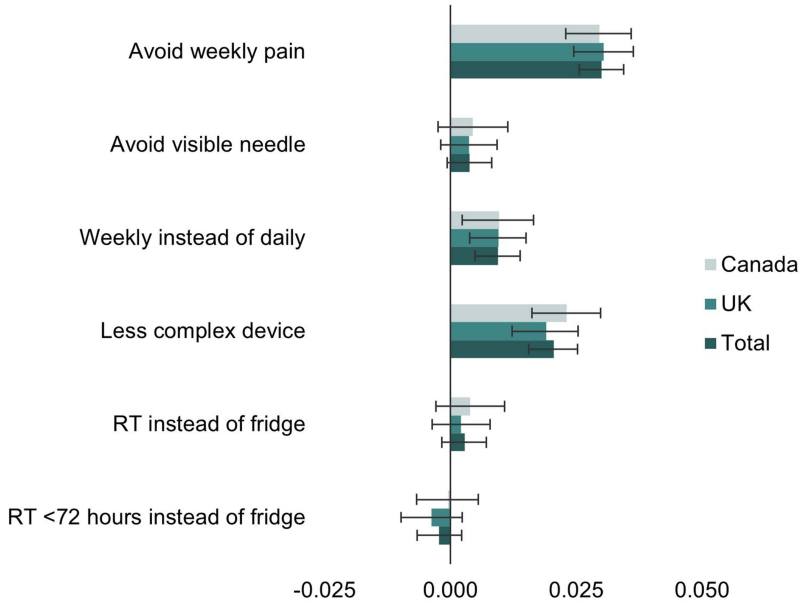

Figure 3 Illustration of utility gain or disutility associated with different aspects of GHD treatment (Survey A).
Abbreviation: RT, Room temperature.

associated with a significant utility gain of 0.009 (95% CI 0.005–0.014, p<0.001) (UK: 0.009 (95% CI 0.004–0.015, p=0.001), Canada: 0.010 (95% CI 0.003–0.017, p=0.008)).

In Survey A, there were no significant results for avoiding a visible needle at the time of injection or for different combinations of storage possibilities (Table 4).

All results for Survey A are illustrated in Figure 3.

TTO Results for Survey B

Table 5 presents utility gains/disutilities associated with the five treatment aspects when the general population evaluated HSs as if they gave injections to a child.

In the analysis, injection pain was considered the most important aspect of GHD treatment in both the UK and Canada. In total, avoiding a weekly injection that causes injection pain to one's child was associated with a utility gain of 0.044 (95% CI 0.038–0.051, p<0.001). In the UK, the utility gain was 0.039 (CI 95% 0.030–0.048, p<0.001), and in Canada the utility gain was 0.050 (CI 95% 0.040–0.060, p<0.001).

When using aggregated data, a less complex injection device and a lower injection frequency were also preferred for caregivers. In total, a less complex injection device was associated with a utility gain of 0.008 (95% CI 0.002–0.014, p=0.006), and weekly instead of daily injections were associated with a significant utility gain of 0.009 (CI 95%

Table 5 Utility Gain or Disutility Associated with Different Aspects of GHD Treatment Elicited with Survey B

	Total			UK			Canada		
	N	Utility	95% CI	N	Utility	95% CI	N	Utility	95% CI
Avoid weekly pain[a]	1106	0.044*	0.038; 0.051	566	0.039*	0.030; 0.048	540	0.050*	0.040; 0.060
Avoid visible needle[b]	579	−0.003	−0.009; 0.003	292	0.002	−0.006; 0.011	287	−0.009	−0.019; 0.0003
Weekly instead of daily[c]	568	0.009*	0.003; 0.014	294	0.004	−0.004; 0.011	272	0.013*	0.005; 0.022
Less complex device[d]	572	0.008*	0.002; 0.014	282	0.007	−0.0003; 0.015	290	0.010*	0.001; 0.020
RT instead of fridge[e]	1128	0.001	−0.005; 0.008	563	0.000	−0.009; 0.008	561	0.003	−0.006; 0.012
RT <72 hours instead of fridge[f]	569	−0.005	−0.011; 0.001	293	0.001	−0.007; 0.008	276	−0.011*	−0.021;-0.002

Notes: *P-value <0.05. [a]HS1 vs HS2, [b]HS1 vs HS3, [c]HS1 vs HS4, [d]HS3 vs HS5, [e]HS4 vs HS6 and HS5 vs HS7, [f]HS1 vs HS8.

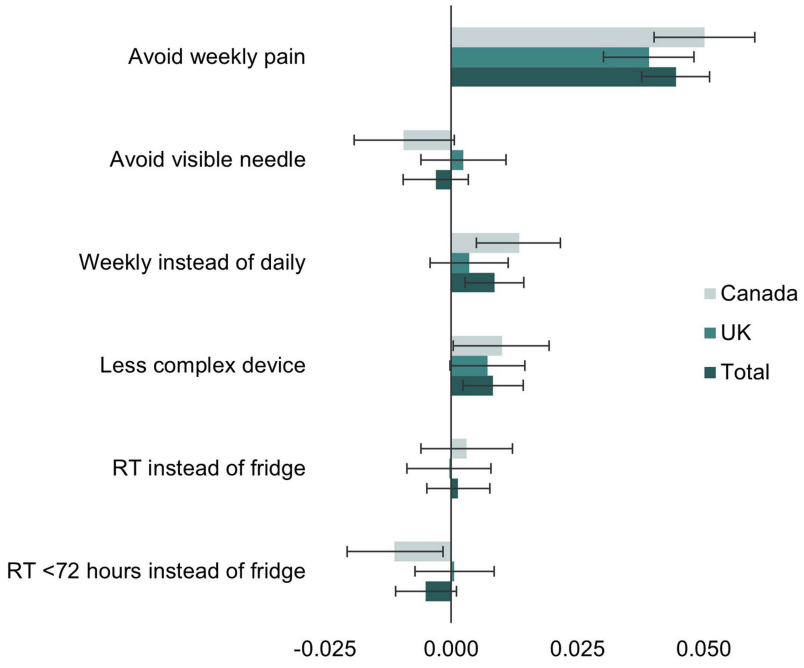

Figure 4 Illustration of utility gain or disutility associated with different aspects of GHD treatment (Survey B).
Abbreviation: RT, Room temperature.

0.003–0.014, p=0.003). When using country-specific data, the utility gains were statistically significant in Canada but not in the UK (Table 5).

Survey B found no significant results for avoiding a visible needle at the time of injection. For different combinations of storage possibilities, the findings in Canada showed that the option of storing the medication at room temperature for up to 72 hours was associated with a significant disutility of −0.011 (95% CI −0.021– −0.002, p=0.019) compared with storage in the fridge. Storage factors were not associated with a utility gain/disutility in the UK or when data from both countries were combined (Table 5).

All results for Survey B are illustrated in Figure 4.

Discussion

This study applied a TTO methodology to estimate utility gains or disutilities associated with GHD treatment for both people living with the disease and potential caregivers. Avoiding weekly injection pain was the aspect associated with the highest utility gain amongst the five evaluated treatment aspects for both people living with GHD and caregivers. Additionally, a less complex device and injection frequency were associated with significant utility gains for both people with GHD and caregivers.

The results emphasise that injection pain is a fundamental aspect of GHD treatment. The importance of injection pain is in line with earlier evidence reporting that 54% of children with GHD describe injection pain as a burden, and 38% of caregivers report that they worry about causing pain to the child.[16] Additionally, the findings suggest that device complexity and injection frequency also have an impact on especially people with GHD. These findings are in agreement with other studies showing that injection devices should be easy and comfortable to use and that "ready to use" devices are preferred amongst people living with GHD.[18,20,21,23,37] Previous studies have also shown that less frequent injections are highly preferred due to greater convenience and reduced life interference.[16,38]

The derived utility for living with or treating a child with GHD is similar to that of living with circulatory system or muscular diseases.[39] More recent studies have also investigated the disutilities for events within other endocrine disorders, including diabetes. In comparison, the findings of this study suggest giving a child weekly painful injections is associated with approximately the same disutility as experiencing monthly non-severe daytime hypoglycaemic events

and a disutility comparable to experiencing a severe hypoglycaemic event once a year when living with diabetes.[40] Avoiding the weekly injection pain when self-injecting is associated with a disutility comparable to experiencing a severe hypoglycaemic event every two years.[40] Additionally, the identified disutility associated with the treatment of GHD is comparable to previous reported decreases associated with the treatment of type 2 diabetes. The study findings suggest that avoiding a complex injection device for the treatment of GHD is associated with a utility gain similar to that of avoiding injections that require reconstitution, waiting time and needle handling for the treatment of type 2 diabetes.[41,42] However, comparisons of utility gains/disutilities between diseases and across different populations should be treated with caution.

Neither needle visibility nor varying storage possibilities were associated with significant utility gains/disutilities in this study. These findings are in opposition to other literature suggesting that needle-free devices are preferred by both people with GHD and caregivers[23] and that refrigeration requirements are burdensome.[16,19,22] The difference in results could be explained by differences in study designs. The current study examines quite different treatment aspects, and some of the HSs include complex and detailed information. In trade-offs where respondents were provided with a lot of information, there is a risk that each respondent will put more focus on specific treatment aspects and potentially neglect the impact of other aspects.

This study was challenged by the currently missing guidelines for measuring and valuing child health. Thus, two surveys taking different perspectives were tested. A very high dropout rate at the beginning of the second survey in the pilot study indicated difficulties amongst respondents in understanding the hypothetical exercise of imagining being diagnosed with GHD at the age of 5. Therefore, the second survey was excluded from the main data collection. Due to the varying findings in the research field and to maintain consistency in measures, it has been recommended to use the adult general population perspective when evaluating children's health.[31] Thus, the utility gains/disutilities elicited using Survey A can be considered a proxy for how different aspects of GHD treatment impact children. As a solution for obtaining more precise estimates when using an adult population as a proxy for child health, quality adjusted life year weighting or deliberation has been suggested.[28] Since there are no clear guidelines for applying this method and no major HTA agencies currently accept this approach as valid evidence, this approach was not applied in the present study.

Based on the findings of this study as well as those of previous studies, people and caregivers who live with GHD seem to face a treatment burden, which should be considered for inclusion in future health economic evaluations and HTA decisions. The findings underline the value of treatment options that are associated with a minimal amount of pain, are easy to use and are administered at a frequency less than daily. Choosing options associated with these features in GHD treatment has the potential to increase HRQoL amongst both people with GHD, including children, and caregivers.

This online TTO survey highlights both strengths and limitations. First, one limitation is that people with GHD and caregivers were not directly included in the development and validation of the surveys. To mitigate this limitation and to ensure that the wording used was representative of the investigated treatment aspects, both clinical experts and findings from a previous qualitative study of the treatment burden for children with GHD and their caregivers were included in the development of the surveys.[16] In addition, the validity of the study findings is enhanced by similar results from the UK and Canada. Second, the approach implies a hypothetical exercise which is not targeted to people with GHD. However, this follows the recommendation from several HTA agencies, including NICE and CADTH, about eliciting HSUVs in a general population.[24–27] The hypothetical approach in the general population provides a large sample size, which provides more robust results. Third, the internet-based design of the study does not provide an opportunity to explain HSs further in case of misunderstandings, and it involves a risk of including respondents who do not accept or understand the premises of the methodology. On the other hand, the approach ensures that HSs are presented in the same way for all respondents, making the trade-offs more comparable. In addition, several features were built into the survey design, making it possible to exclude respondents who did not understand or accept the methodology. Finally, the study design might have caused bias in the results if internet users in general evaluate HSs differently from non-internet users. Since the UK and Canada have a 98% and a 94% internet accessibility rate, respectively, that poses a minor limitation.[43] At the same time, the internet-based approach increases the opportunity for obtaining a representative sample compared with an interview-based design.

Conclusion

This study finds that several aspects of GHD treatment are associated with a significant impact on the associated HSUVs amongst both people living with GHD, including children, and potential caregivers. Based on the results, obtained from a large sample of respondents from the UK and Canada using an online TTO survey, treatment options without (1) injection pain, (2) a time-consuming and complex injection process and (3) daily injections are associated with utility gains. Therefore, these treatment aspects could be expected to result in higher HRQoL.

These study results can be used to inform future economic evaluations of GHD treatment. In addition, the study may inform future treatment choices.

Abbreviations

CADTH, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; ESOMAR, European Society for Opinion and Market Research; GH, growth hormone; GHD, growth hormone deficiency; HRQoL, health-related quality of life; HS, health states; HSUV, health state utility value; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; RT, room temperature; TTO, time trade-off.

Data Sharing Statement

Not applicable. The datasets generated and/or analysed during the current study are not publicly available because the respondents were promised full anonymity.

Acknowledgments

Interim findings of this study were presented at ISPOR 2023 as a poster presentation. The poster's abstract was published in Value in Health, Volume 26, Issue 6, S312: https://www.valueinhealthjournal.com/article/S1098-30152301883-1/fulltext.

The authors gratefully acknowledge Professor Donna Rowen for her valuable input regarding how to measure and value child health. Additionally, the authors acknowledge EY for the medical writing of the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Novo Nordisk, 2860 Søborg, Denmark.

Disclosure

LJ and JHB are employees of Novo Nordisk. AO and CY are employees of EY, which is a paid vendor of Novo Nordisk. SK and GB have served as scientific advisory for Novo Nordisk. The authors report no other conflicts of interest in this work.

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