Patient Preference and Adherence

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ORIGINAL RESEARCH

Developing a Process for Preference Measures in Pediatric Growth Hormone Deficiency: Challenges and Solutions

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Purpose: Patient experience data capturing the patient voice is gaining increasing recognition across the drug development continuum for use in risk/benefit analysis to evaluate new drugs. The aim of this study was to delineate a prototype process for and then, following this process, develop questionnaires to rigorously assess patient-centric treatment preferences, using pediatric growth hormone deficiency (PGHD) treatment as a model.

Patients and Methods: A literature review and concept elicitation interviews with clinical experts (n=5), caregivers of children with PGHD (n=15), and children with PGHD (n=15) were conducted. Most respondents were on injectable treatments with a small subsample on an investigational oral treatment. Data were analyzed based on adapted ground theory, and the GHD-Preference Measure (GHD-PRM), and GHD-Attribute Measure (GHD-ATM) were developed. These questionnaires were cognitively debriefed, refined, and finalized. Best practices for patient-reported outcome measure development and guidelines on assessing patient preferences were followed.

Results: Beyond efficacy, some of the most important treatment aspects determining preference for caregivers were the ease of preparation/setup, convenience, and side effects. The most frequently reported reasons for missing, postponing, or changing their child's medication (eg, dosage) included travel/being away from home and flexibility of dosing. The most frequently reported treatment impacts on children's daily lives were travel/being away from home, social activities/relationships, and evening routine/schedule. Findings were generally similar between caregivers and children, and those on injectable vs oral treatment. The GHD-PRM is intended for use when treatment comparisons are appropriate; the GHD-ATM is intended for use when treatment comparisons are not available. Each has a caregiver and child version.

Conclusion: The GHD-PRM and GHD-ATM can be considered disease-specific prototype preference and attribute questionnaires developed according to a rigorous patient-centric process. Novel, well developed preference measures such as these can provide valuable data to researchers, clinicians, regulators and reimbursement agencies.

Keywords: human growth hormone deficiency, quality of life, patient preference, surveys and questionnaires, attribute measure

Introduction

Patient experience data (PED) capturing the patient voice is gaining increasing recognition to provide potential evidence across the drug development continuum and for use in risk/benefit analysis to evaluate new drugs and inform reimbursement and pricing decisions.

Patient experience data is defined as data that are collected by any persons and are intended to provide information about patients' experiences with a disease, treatment, or condition and includes the experiences, perspectives, needs, and priorities of patients.[1] The United States (US) Food and Drug Administration's (FDA) position on the importance of PED

Received: 9 November 2024
Accepted: 21 April 2025
Published: 8 May 2025

is echoed by the European Medicines Agency, which states, "Throughout the drug development process, working with patients and caregivers to learn about patient perspectives can be valuable in addressing specific questions to inform development programs and related regulatory decision making".[2]

One type of PED is patient treatment preference information (PPI) which includes factors such as efficacy, side effects, and impacts on daily life and functioning. PPI defined by the FDA guidance is the relative desirability (what is valued most) or acceptability (perspective on risk/benefit) to patients and care-partners of alternative health interventions. Simply defined, PPI evidence is an assessment of acceptability of drug A compared to drug B, based on rating desired attributes.[3,4] Methodologies for assessing preference can be either qualitative or quantitative, ranging from focus groups to discrete choice experiments, with approximately 32 different methodologies identified in the research literature.[4,5] Many of these methods may require a person to make a series of judgments regarding treatment attributes in "trade off" scenarios which can be complex to design and have been criticized for being difficult for patients to complete and for policy makers to interpret.[6,7] Further, some conjoint analysis preference methodologies require stated preferences for hypothetical scenarios based on attributes which may or may not have been experienced by the person completing the questionnaire.[8,9] Although no one methodology may be applicable across the drug development process, greater debate and consensus on methodology for the development and use of PPI questionnaires in a systematic and scientifically valid way is needed.[10–12]

Pediatric growth hormone deficiency (PGHD), is a rare condition that occurs when inadequate growth hormone (GH) is produced. Patients with PGHD typically experience growth failure with potential psychosocial impacts. They may also face long-term health risks, including increased abdominal fat from altered lipid metabolism, dyslipidemia (elevated LDL, triglycerides, reduced HDL), decreased lean body mass, and reduced bone density.[13] The standard-of-care treatment for PGHD is daily subcutaneous (SQ) injections of recombinant human GH. Long-acting GH therapies providing a once weekly SQ injection anytime during the day have recently been approved.[14–16] In addition, novel oral GH secretagogues are currently being investigated. Each therapy has a different mode and timing of administration and scheduling requirements. Thus, understanding preferences for PGHD treatment can be a critical factor in improving treatment adherence,[17,18] evaluating the treatment risk/benefit profile, and providing evidence for regulatory, clinical practice, and pricing decision-making. There are limited disease-specific measures of treatment preference for PGHD available, and those available either do not ask about the attributes which form preferences or have not been developed including the patient voice.

The aim of this study was to delineate a rigorous prototype process for developing easily administered and interpretable patient-centric treatment preference questionnaires, which can be used when respondents have experienced either one or multiple treatment options. Pediatric growth hormone deficiency treatment was used as a model for the study.[19] This process draws from aspects of best practices for patient-reported outcome (PRO) measure development,[20] as well as the underlying concept of attributes on which preferences are based on in discrete choice methodologies. Child GH treatment is used as the case study for the questionnaires' development.

Methods

Independent Review Board (IRB) approval for study protocol LP22-PGHDPrefQ (IRB Tracking Number: 20230357) was received from WCG IRB. The research was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent included participant's agreement to publication with individual identities remaining confidential.

Establishing Content Validity Process

Methodology for this study included a literature review and concept elicitation (CE) interviews with clinical experts, caregivers of children with PGHD, and children with PGHD. These data were analyzed and used to develop a treatment preference questionnaire and a treatment attribute questionnaire. Intended meanings of all instructions and items were described in a draft item definition table. These questionnaires then underwent a transability assessment, cognitive debriefing (CD) assessment, were refined, and finalized. The item definition tables were developed to assist with interpretation of items for translators by providing definitions and intended concepts for all instructions and items, as well as lists of alternative wording when required for a given language. The study process flow chart is presented in Figure 1.

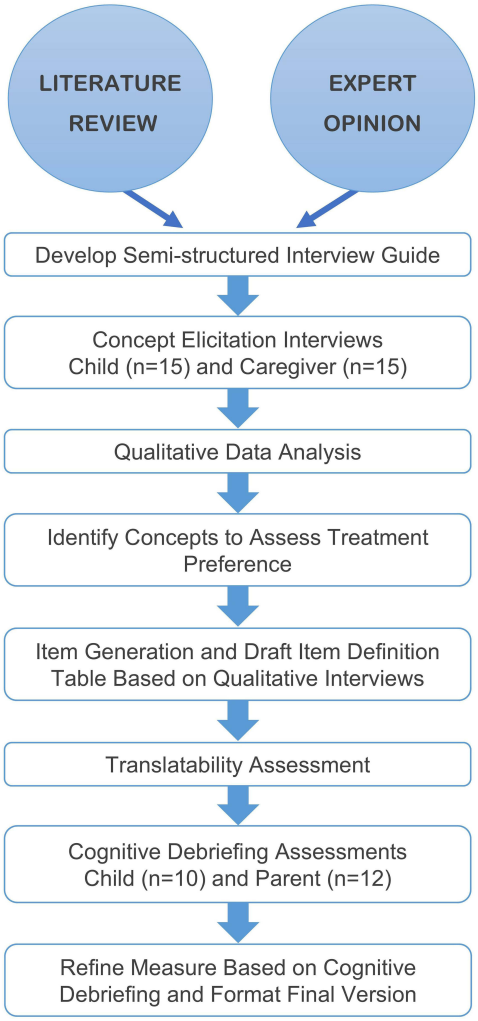

Figure 1 Study Process Flow Chart. Concept Elicitation and Cognitive Debriefing Assessment (Content Validity).

Literature Review

A literature review was conducted to search for relevant medical and social science literature. The PubMed (NLM) and EMBASE (ProQuest) databases were searched using terms and variant spellings of terms and appropriate subject headings/subheadings when possible. The key search terms included: preference, patient preference, rating scale, method, survey, measure, questionnaire and/or growth hormone deficiency. The literature review was used to inform the development of the semi-structured interview guides for the CE interviews.

Participant Recruitment and Eligibility Criteria

Recruitment

Caregiver and child participants were recruited from private practice pediatric endocrinologists or from clinical sites participating in a Phase 2 trial of an investigative oral treatment for PGHD (LUM-201-01 Trial; NCT04614337; Clinical Trials.gov; https://www.clinicaltrials.gov/; registered on 02 November 2020) and by a professional recruitment agency using their proprietary databases (patient panels) as well as via clinicians and advocacy groups. Confirmation of growth hormone deficiency (GHD) diagnosis in the form of a GH medication label, or a letter/clinic note from a healthcare provider confirming the child's diagnosis, was required for any participants not referred by a physician.

Eligibility Criteria

Clinical expert participants were pediatric endocrinology physicians (MD) or nurse practitioners (NP) with at least 5 years of experience in the specialty and caring for a minimum of 25 children with GHD in a clinical setting. Experts were

https://doi.org/10.2147/PPA.S500330

interviewed to gain a deeper understanding, from the clinical perspective, of the preferences, likes, and dislikes that caregivers and children have for PGHD treatment.

Eligibility criteria for children and caregivers were the same for all recruitment sources for both the CE interviews and the independent sample for the CD assessment interviews. Eligible caregivers were the caregiver of a child with a diagnosis of idiopathic GHD aged ≥ 3 years and aged ≤ 11 years (girls) and ≤ 12 years (boys). Caregivers were required to be currently living with the child, actively involved in the child's day-to-day care and GHD treatment, willing to provide informed consent to participate in the interview, and able to read and communicate in English. Eligible children had a diagnosis of idiopathic GHD, were aged ≥ 10 years and aged ≤ 11 years (girls) and ≤ aged 12 years (boys), before bone growth plate closure had occurred, and were able to read and communicate in English.

Concept Elicitation Interview Data Collection

Concept elicitation data were collected via individual telephone interviews or virtually by video conference (cameras off), using semi-structured interview guides. The interview guides used open-ended questions to elicit experiences related to the child's PGHD treatment. Questions were framed to query what attributes of treatment were preferred (liked vs disliked) in terms of the three pillars of treatment satisfaction (convenience, efficacy, and side effects)[21] as well as interference in daily life, impacts on emotional well-being, and treatment compliance. Interviews were iterative where information from interviews was used to inform subsequent interviews. Interviews lasted approximately 60 minutes and were audio recorded and transcribed verbatim. Interviews were conducted by two experienced qualitative researchers who participated in a training to ensure similarity in how questions and probes in the interview guide were asked. Additionally, they met regularly to compare interview notes and any revisions needed.

Concept Elicitation Interview Qualitative Data Analysis

Data from the CE interviews were analyzed based on an adapted grounded theory approach.[22,23] Adapted grounded theory is a methodology in which concepts and theory are developed in a manner that is "grounded" in the qualitative data analysis based on participants' words and meanings, while acknowledging existing clinical and expert knowledge. All interview transcripts were analyzed for content by theme using the Dedoose qualitative and mixed methods analysis software program (Dedoose© Version 9.0.90 2023). A preliminary code list was constructed and then emerging concepts that arose during the coding process were added, and previously coded transcripts were evaluated for new concepts. Throughout the coding process, concepts/codes were organized into categories encompassing larger themes and sub-themes. Thematic saturation analysis was conducted separately for child and caregiver interviews to ensure that all important and relevant concepts were covered and considered reached when 95% of concepts were covered. All coding and analysis were conducted by the same person.

Item Generation and Translatability Assessment

An item generation meeting was then held with the entire research team to review the analysis of the CE data and generate draft items for the measures. These drafts then underwent a translatability assessment to determine if the words used could be easily translated into non-English languages.

Cognitive Debriefing Assessment Interview Data Collection

The draft measures then underwent cognitive debriefing assessment. Individual interviews were conducted with caregivers and children by telephone or virtually by video conference (cameras off) and lasted approximately 60 minutes. Participants' thoughts on the meaning of all instructions and items were elicited and compared to the intended meanings outlined in the draft item definition table. A "think aloud" method, as well as verbal probing, was used to ask respondents questions regarding the relevance and importance of the questionnaires' items and the meaning of items and instructions.

Assessment interviews were conducted in blocks of 3 participants. After a block was completed, the findings were reviewed and suggested modifications were identified. An updated version of the questionnaire was then created for use in the following block. This process repeated until it was determined that the readability and relevance were acceptable based on consensus agreements among respondents in an entire block. The decision to change an instruction, item, or response option wording on the questionnaire was typically made when 2 participants had similar comments or if the change was viewed as an improvement.

Results

Expert Interviews

Five clinical experts (3 MDs and 2 NPs) participated in individual interviews. The experts had a mean of 16.4 years' experience practicing in their current specialty (SD, 7.5; range, 7–28). Three (60.0%) worked in private practice, and two (40.0%) worked in a hospital setting. On average, experts spent most of their time in clinical practice (66.0%, SD, 31.3), followed by research (23.0%, SD, 18.6), teaching (7.0%, SD, 13.0), and other tasks (4.0%, SD, 8.9). The estimated percentage of their patients who were diagnosed with idiopathic PGHD averaged 74.4% (SD, 30.0; range, 40–97).

Expert Interview Findings

Experts reported on their own and their patients' treatment preferences and issues. Table 1 provides a summary of results.

Table 1 Expert Interview Findings

Concept	Findings	Exemplary Quotes
Treatment preferences	Expert clinicians indicated that they most preferred PGHD treatments that were effective, easy to use/administer, and affordable/covered by health insurance. According to experts, children's and caregivers' most preferred PGHD treatment characteristics included treatments that were easy to use/administer, had less frequent injections, had easy preparation/setup, and had easy storage/refrigeration.	*Number one, it must work. And it must be safe. So, safety and efficacy. Number two, ease of administration…obviously there's no oral that's FDA approved…the device must be easy to use. So, you know, all-inclusive sort of pen devices are easier than needles and syringe, and having to draw it up. So, it comes down to number one, efficacy; number two, safety; and probably number three, convenience. (MD)*
Treatment convenience/ease of use	Injectable PGHD treatment inconveniences frequently reported by experts included storage/refrigeration requirements, frequency of administration, preparation/setup needed, the needles/injections used for administration, and challenges with travel/being away from home. Few inconveniences of oral investigational PGHD treatment were reported.	*Convenience in terms of…preparation…if there's the least amount of preparation involved is, you know, by far the easiest, because some of these kids are giving the medication themselves, so if there's a lot of preparation, that's definitely one of the factors that are involved. Um, refrigeration is another, you know, factor, if they have to refrigerate it, and some of these kids are traveling in camp and things like that that's certainly another, you know, um, factor in terms of ease. (NPr)*
Treatment efficacy	All experts indicated that PGHD treatment efficacy was important or very important for child and caregiver treatment satisfaction. The most important treatment efficacy factors affecting caregiver satisfaction, according to clinicians, were growth velocity/rate and general growth/getting taller.	*…[Parents] notice how much their child's growing, and that's what they're excited to talk about. And, um, so I–I definitely think that's extremely important to people. (MD)*
Treatment side effects and complications	Most clinicians described treatment side effects as important or very important for child and caregiver treatment satisfaction. The injectable PGHD treatment side effects that clinicians discussed most frequently were pain/discomfort at injection site, joint/bone pain, and headaches. The one side effect of oral PGHD investigational treatment mentioned by one of the 2 experts with experience prescribing oral treatments was increased appetite. The frequently mentioned complications and documented side effects of injectable PGHD treatment included slipped capital femoral epiphysis, scoliosis, increased intracranial pressure, weight gain, and a potential risk of cancer. Among these, weight gain was the sole reported adverse event complication of oral investigational PGHD treatment.	*So, with injectables, by far the most common side effects are…pain or redness at the injection site…like, local injection-site reactions, which are usually mild. But that's the most common side effect. Like, any of the other side effects are very rare, although can be serious – but are very rare. (MD)* *…we have certainly heard of patients having headaches. We've had patients with swelling. We've had patients with joint pain…we've had patients with…SCFE…slipped capital femoral epiphysis…. worsening scoliosis. (NP)* *…with the orals, I would say the most common side effect we've been seeing is the increased appetite. (MD)*
Treatment compliance	Clinical experts reported a wide range of treatment adherence rates for children taking PGHD medication. The most frequently discussed reasons for missed, postponed, or changed medication doses included travel/being away from home, cost/insurance coverage issues, forgetting, injection fatigue, drug/device supply shortages, and lack of caregiver supervisions of treatment. The PGHD medication features that clinicians most often pointed to as making it easier to use medication as prescribed were the device/pen, ease of use/administration, less frequent administration, and no/limited side effects.	*Interviewer: And what are some reasons given for missed doses or for not giving as prescribed?* *Expert: Yeah. So, uh, injection fatigue…travel, sleepovers, um, the child had an illness that night. Um, simply forgetting…with a busy schedule. (MD)* *Interviewer: So, what are the features of GHD medication that make it easier…to use as prescribed?* *Expert: I think the convenience of the device itself…for the injectables. I think that oral will make it easier, uh, compared to an injectable….I think that… the number of pills will affect…how easy it is to comply. The frequency of dosing – so, you know, weekly versus daily for the injections. Weekly it's easier. (MD)*

(*Continued*)

https://doi.org/10.2147/PPA.S500330

Table 1 (Continued).

Concept	Findings	Exemplary Quotes
Treatment interference in daily life	Experts reported PGHD treatment interference in the daily lives of both children and their caregivers. The most reported impacts on children's daily lives were impacts on social activities/ relationships, travel/being away from home, evening routine/ schedule, and school/camp. The most often discussed impacts of treatment on caregivers' daily lives were the added burden/ responsibility of treatment and managing their child's emotions/ resistance to treatment.	*So, when [children] have birthday parties and sleepovers, um, they have to be pulled aside, um, and given the injection where their friends are still having fun. (MD)* *…the negative [for caregivers] is the-the burden of having the medical treatment – the follow-ups, the injections…and of course…all of the difficulty with… insurance authorization and the logistics of having the medication approved. (MD)*
Treatment impacts on emotional well-being	Clinical experts observed many different impacts of PGHD treatment on children's and caregivers' emotional well-being. The most frequently reported impacts of PGHD treatment on children's emotional well-being included feeling fearful/scared, positive feelings (such as increased self-esteem or confidence), resistance/avoidance of treatment, not wanting others to know about treatment, hate/dislike of treatment, and feeling anxious/ nervous. The most often mentioned PGHD treatment impacts on caregivers' emotional well-being were resistance/avoidance of treatment and feeling worried/concerned.	*…there's anxiety regarding the injections…And so, um, with all of that, umm, sometimes it's a challenge to give a daily injection, particularly to the smaller children at bedtime. (MD)* *…when the kids start growing, their confidence grows… they're… better able to tolerate the teasing they get from being small because they now know the problem is being fixed. And they're going to grow and be bigger. (MD)* *…if a kid doesn't like [the treatment],… and it becomes a struggle and a fight to take it… then parents start to avoid it. (MD)*
Influences of culture, race/ ethnicity, and gender on treatment preferences	Clinicians described several factors related to culture, race/ ethnicity, and gender that may affect PGHD treatment preferences and experiences. The most often discussed cultural influences were the social stigma of PGHD treatment, distrust of the medical establishment/treatment, socioeconomic background/education of caregivers, and the culture surrounding competitive sports. Factors related to racial/ethnic background that were noted to influence PGHD treatment preferences included the importance of stature/height, racial/ethnic disparities in diagnosis/treatment, and distrust of the medical establishment/treatment. Clinicians also noted gender disparities in the diagnosis and treatment of PGHD, as well as views on gender and height, both of which may impact PGHD treatment preferences and experiences.	*I mean, there are always cultural things that come up, you know. For example, in cultures or religions in which arranged marriages are, nobody wants anyone to know that the kids have something wrong with them because then they might be perceived as less marry-able. (MD)* *There are certain… ethnicities where people are smaller, and it's not as much of a big deal. And then there are others where they put a lot more… emphasis on height. …so, I definitely think that all of those things play huge roles in influencing whether people… choose to pursue, uh, treatment at all. (MD)* *…more boys are referred for short stature than girls. But the reality is-is that the rate of short stature is equal in both genders. So, you know, why is that? That's a health…care inequity…for girls…people say,* "She's small. It doesn't matter". *(MD)*

Abbreviations: MD, Doctor of Medicine; NP, nurse practitioner.

Caregiver Concept Elicitation Interviews

Sample Description

Table 2 presents the demographic characteristics of 15 caregivers of children with GHD who completed a CE interview and the demographic and general health characteristics of the children of caregiver interview participants.

Caregiver Interview Findings

Thematic saturation was assessed for the 15 caregiver interviews and identified 171 different concepts related to their general experiences with and preferences for GHD treatment for their children. Following the 14th caregiver interview, 165 concepts (96.5%) were mentioned, and thematic saturation was considered reached.

Based on the caregiver transcripts' analysis, a wide range of treatment-related preferences, experiences, and impacts were identified. Table 3 presents a summary of the findings for themes and exemplary quotes.

Child Concept Elicitation Interviews

Sample Description

Table 4 presents the demographic characteristics of 15 children with GHD who participated in a CE interview and the caregiver-reported general health characteristics of the child interview participants.

Table 5 presents the demographic characteristics of the caregivers of the children who completed a CE interview.

Table 2 Demographic Characteristics and General Health Characteristics

Demographic Characteristics: Caregiver Concept Elicitation Participants	**Total (*n*=15)**
Caregiver age (years)	
Mean(SD)	40.3 (5.4)
Range	31–50
Caregiver relationship to child, n(%)	
Mother	13 (86.7)
Father	2 (13.3)
Caregiver marital status, n(%)	
Married/partnered	13 (86.7)
Divorced	2 (13.3)
Caregiver race/ethnicity, n(%)[a]	
White/Caucasian	13 (86.7)
Asian	2 (13.3)
Latino or Hispanic	2 (13.3)
American Indian or Native Alaskan	1 (6.7)
Combined yearly household income, n(%)	
Less than $50,000	1 (6.7)
$50,000 to $74,999	1 (6.7)
$75,000 to $99,999	3 (20.0)
$100,000 to $149,999	3 (20.0)
More than $150,000	7 (46.7)
Demographic Characteristics: Children of Caregiver Concept Elicitation Participants	**Total (*n*=15)**
Child age (years)	
Mean(SD)	8.4 (2.6)
Range	4.3–11.6
Child gender, n(%)	
Male	9 (60.0)
Female	6 (40.0)
Health Background Characteristics: Children of Caregiver Concept Elicitation Participants	**Total (*n*=15)**
Child age (years) at GHD diagnosis	
Mean(SD)	5.5 (2.5)
Range	1.3–10.0
Child age (years) started first prescription PGHD medication	
Mean(SD)	5.7 (2.4)
Range	1.4–10.0

(*Continued*)

https://doi.org/10.2147/PPA.S500330

Table 2 (Continued).

Current PGHD treatment, n(%)	
Injectable[b]	13 (86.7)
Oral	2 (13.3)
Frequency child's current prescription PGHD medication, n(%)	
Daily	3 (20.0)
6 days/week	11 (73.3)
Weekly	1 (6.7)

Notes: Percentages may not add to 100 due to rounding. [a]Response categories are not mutually exclusive, so percentages do not add to 100.
[b]All injectable PGHD medication was administered with an injection pen.
Abbreviations: SD, standard deviation; GHD, growth hormone deficiency; PGHD, pediatric growth hormone deficiency; US, United States.

Table 3 Caregiver Interview Findings

Concept	Findings	Exemplary Quotes
Treatment likes/ dislikes	In terms of injectable treatment likes, caregivers of children receiving injectable PGHD treatment (86.7%, n=13) most frequently reported liking their treatment device/pen (53.8%, n=7), the ease of preparation/setup (46.2%, n=6), the medication being quick/easy to administer (38.5%, n=5), and treatment efficacy (30.8%, n=4). Frequently mentioned dislikes included the needle/ injection (46.2%, n=6), difficulty of administration (38.5%, n=5), and difficulty of travel/being away from home (30.8%, n=4). Oral treatment likes mentioned by caregivers of children receiving oral investigational PGHD treatment (13.3%, n=2) included the tablet form (100.0%, n=2), no injections (100.0%, n=2), no child complaints (50.0%, n=1), the time of day/schedule (50.0%, n=1), flexible time of administration (50.0%, n=1), and quick/easy administration (50.0%, n=1). Insufficient tablet coating (50.0%, n=1) was the one dislike of oral investigational treatment discussed.	*…I like the pen that we use. It's super easy. You just dial it and push. So that has been great. (mother of 7-year-old boy, injectable treatment)* *I like that…[the medication] comes like in the pen. I don't have to… mix anything, or…draw any medication out. It's just ready to go. Obviously, I have to…prime it, I guess, before use…But, I mean, that's easy-peasy. (mother of 4-year-old boy, injectable treatment)* *…[There are] emotional things coming along with injections. Even once you get used to them, it's still kind of hard to do an injection. (mother of 9-year-old girl, injectable treatment)* *I dislike that it's a nightly injection. (mother of 6-year-old boy, injectable treatment)* *…[My child] is young. So, I think…not having to do injections every single day…even though he did well with it, I'm seeing with him that he's really…appreciating having a break from…that…. he d-does really well with swallowing the pills. And…we also like that [treatment is administered] in the morning as opposed to right before bedtime. (mother of 5-year-old boy, oral investigational treatment)*
Treatment convenience/ ease of use	More than half of caregivers indicated that convenience (60.0%, n=9) was important or very important in their PGHD treatment satisfaction. For caregivers of children receiving injectable PGHD treatment (86.7%, n=13), the most often mentioned convenience/ease of use factors associated with treatment included the device/pen (69.2%, n=9), time of day/schedule of dosing (61.5%, n=8), adjusting/calculating doses (61.5%, n=8), and preparation/setup (53.8%, n=7). The treatment inconveniences/difficulties most frequently discussed included travel/being away from home (92.3%, n=12), storage/ refrigeration (84.6%, n=11), insurance coverage issues (69.2%, n=9), child emotions/discomfort (69.2%, n=9), and drug/device availability/access (61.5%, n=8). For caregivers of children receiving oral investigational PGHD treatment (13.3%, n=2), the most frequently reported convenience/ease of use factors were the time of day/schedule of dosing (100.0%, n=2), the packaging (100.0%, n=2), storage/refrigeration requirements (100.0%, n=2), and the tablet form (100.0%, n=2).	*The most convenient part about [the treatment] is just the actual device itself. It's…prepackaged. It's nice to go. You just put the needle on there. It's-It's good to go. (mother of 5-year-old girl, injectable treatment)* *Thankfully, time of day with the medications we've been on, they said we could really choose. It could be a morning one day, it could be evening one day. So that has been nice having that flexibility. (mother of 4-year-old boy, injectable treatment)* *…I would say travel is a little tough… just through the airport…we were somewhere then, uh, the ice pack was too big, so they confiscated the ice pack... That's been the hardest thing. Or just keeping it, you know, refrigerated when we're traveling. (mother of 9-year-old girl, injectable treatment)* *It was extremely convenient…the pills are so small he had no issues swallowing it…you only have the one tiny, little bottle. You can take it with you wherever you're going…His dad and I…are not married so it was easy for us to divide the pills and…keep one bottle at his dad's house and one bottle at my house…so that was very convenient for us as well. It's only a one time a day thing. You don't have to do it more than once a day…It was all very easy and convenient. (mother of 8-year-old boy, oral treatment)*

(*Continued*)

Table 3 (Continued).

Concept	Findings	Exemplary Quotes
Treatment efficacy	All caregivers (100.0%, n=15) indicated that treatment efficacy was important or very important in determining their satisfaction with their child's treatment. When asked what they consider when deciding on their satisfaction with the efficacy of their child's PGHD treatment, caregivers most often mentioned child's growth/getting taller (100.0%, n=15), child health (73.3%, n=11), child's growth velocity/rate (66.7%, n=10), child's social well-being (46.7%, n=7), and child's emotional well-being (40.0%; n=6).	*Oh, well, [efficacy is] very important…I wouldn't want to be giving my kid a shot if it wasn't working. (father of 11-year-old boy, injectable treatment)* *…his height and his weight have been like progressing on a really nice curve, like what you want to see, like a normal kid, you know their growing is progressing completely normal, which was awesome because you know before we started the treatment…he really wasn't having any kind of a growth curve. (mother of 7-year-old boy, injectable treatment)* *…the priority is her just having her growth hormone medication…so that she can grow and be healthy. (mother of 8-year-old girl, injectable treatment)*
Treatment side effects	Most caregivers reported that side effects (80.0%, n=12) were important or very important in their satisfaction with their child's PGHD treatment. The most frequently reported side effects for children receiving injectable PGHD treatment (86.7%, n=13) were pain/discomfort at injection site (69.2%, n=9), swelling/bruising at injection site (30.8, n=4), and tiredness (15.4%, n=2). Among caregivers of children receiving oral investigational PGHD treatment (13.3%, n=2), 1 caregiver reported that their child experienced an increased appetite (50.0%, n=1) due to their medication.	*…[Side effects are] very important…if he was having major side effects…we would really have to think hard about continuing the treatment. (mother of 11-year-old boy, injectable treatment)* *…just a little bit of bruising. He's a very muscular kid. He doesn't have really – about an ounce of fat on him. I mean, he's, he's just a really lean kid, so he does get some bruising at his injection sites. And that's about the only side effect… (father of 11-year-old boy, injectable treatment)* *The pen really seems to have some force behind it…when you inject it…he says that it hurts. (mother of 4-year-old boy, injectable treatment)*
Treatment compliance	All caregivers of children receiving injectable PGHD medication (86.7%, n=13) reported missing, postponing, or changing their child's treatment in the past. The most frequently reported reasons for missing, postponing, or changing their child's medication (eg, dosage amount) included travel/being away from home (84.6%, n=11), flexibility of dosing if miss/skip a dose or pen runs out (76.9%, n=10), forgetting (69.2, n=9), and time constraints/schedule (69.2%, n=9). Among caregivers of children receiving oral treatment (13.3%, n=2), 1 caregiver reported missing/postponing their child's medication (50.0%, n=1). Reasons for missing or postponing oral treatment included flexibility of dosing and forgetting.	*We usually take Saturdays off [for treatment]… it's pretty easy to switch that day, or honestly, what our doctors have told us…There have been times where we've just flat out forgotten to do one another day of the week, and so we just switch it. Or, like, if we do travel and it's just not going to be convenient to take it with us, and he misses, say, you know, two or three days, then we-we have been told that what we can do is add a little bit – like, to split that missed dosage among other days. So, we just add a little bit to a day that we are doing the dose. (mother of 11-year-old boy, injectable treatment)* *Dad will forget to give [the treatment injection] on…his night…And so that sometimes does happen. And then the night that should have been the night off, like on a weekend, I will have to give it to [daughter] on that night. (mother of 5-year-old girl, injectable treatment)*
Treatment preferences	When questioned about what features they would like in a preferred PGHD medication for their child, caregivers (n=15) most often mentioned efficacy (66.7%, n=10), tablet form (60.0%, n=9), less frequent administration (46.7%, n=7), no/little side effects (40.0%, n=6), quick/easy to administer (46.7%, n=7), not refrigerated (40.0%, n=6), and no needle/injection (33.3%, n=5). Most caregivers reported that they would prefer a treatment that stimulates their child's growth hormone production (66.7, n=10) over a treatment that replaces growth hormone (6.7%, n=1). When asked about whether they would prefer a daily oral or a weekly injectable PGHD medication, more than half of caregivers reported preference for the daily oral treatment (53.3%, n=8). The most frequently reported reasons for preferring daily oral treatment among those indicating this preference were child fear/dislike of needles or injections (37.5%, n=3), being less likely to forget a daily dose (37.5%, n=3), ease of administration (25.0%, n=2), and the routine/consistent schedule (25.0%, n=2). Fewer caregivers expressed a preference for a weekly injectable PGHD medication (33.3%, n=5), and for 2 caregivers, preference would depend on various factors, such as child age (13.3%, n=2).	*…if he is taking medication, I would want it to work and benefit him. So that might be, probably, the most important thing for me… (mother of 5-year-old boy, oral treatment)* *…maybe a pill so I wouldn't have to poke him, and…I wouldn't have to carry a cooler with us. And it would be, it would be less painful for him and more convenient for me, I guess. (father of 11-year-old boy, injectable treatment)* *Interviewer: …if you could choose between weekly injections or daily oral tablets by mouth for your child growth hormone deficiency medication which would you prefer and why?* *Interviewee: I would do the oral tablets. Both because I think it would be easier just, you know he would just take a pill as opposed to have to have an injection, and I think the daily would be less [likely forgotten]. (mother of 7-year-old boy, injectable treatment)* *[I would prefer] the oral daily [as opposed to weekly injections] just because I don't think he enjoys the injections. (mother of 11-year-old boy, injectable treatment)* *I mean, as long as my kid doesn't mind it by mouth, that would be perfect, you know? If it tasted great and they could do it, I mean, that would be the preferred [treatment, as opposed to weekly injections]. (mother of 10-year-old girl, injectable treatment)*

(*Continued*)

https://doi.org/10.2147/PPA.S500330

Table 3 (Continued).

Concept	Findings	Exemplary Quotes
Impacts on child's daily life	Among caregivers of children receiving injectable PGHD treatment (86.7%, n=13), the most frequently reported treatment impacts on children's daily lives were travel/being away from home (92.3%, n=12), social activities/relationships (46.2%, n=6), and evening routine/schedule (30.8%, n=4). Among caregivers of children receiving oral investigational PGHD treatment (13.3%, n=2), limited treatment impacts on children's daily life were reported, including impacts on schedule/routine (50.0%, n=1) and school/camp (50.0%, n=1).	*…we love to go like camping and hunting and fishing. So, you have to keep those injections cold. And so just…having them in their cooler and making sure that you have enough ice to last you however many days we're going to be out there, that can be challenging sometimes. (father of 11-year-old boy, injectable treatment)* *I wouldn't say [the treatment is] convenient...it's hard. It's like she wants to do sleepovers, and…we have to always keep that stuff in mind. (mother of 9-year-old girl, injectable treatment)*
Impacts on child's emotional well-being	The most often mentioned impacts on children's emotional well-being associated with injectable treatment (86.7%, n=13) were feeling anxious/worried (69.2%, n=9), acceptance/being "used to" treatment (69.2%, n=9), and resisting/avoiding treatment (61.5%, n=8). Among caregivers of children treated with oral PGHD treatment (13.3%, n=2), the most often mentioned impact on children's emotional well-being was positive feelings (eg, feeling happy about treatment) (100.0%, n=2).	*…right before we give the shot every day he expresses some sort of like,* "Oh, it's going to hurt". *Or like some sort of expression of like anxiety about being poked with a needle. (mother of 6-year-old boy, injectable treatment)* *In the beginning, yes, every night it was a fight. But now, not really. I mean, I don't think he has ever, like, been grumpy about his injection anymore. He's pretty used to it now. (mother of 7-year-old boy, injectable treatment)*
Impacts on caregivers	For caregivers of children receiving injectable PGHD treatment (86.7%, n=13), the most frequently discussed PGHD treatment impacts on caregivers were added burden/responsibility (92.3%, n=12), interference in daily activities/life (38.5%, n=5), managing child emotions/resistance (38.5%, n=5), relationship with spouse/partner (38.5%, n=5), and family activities/relationships (38.5%, n=5). For caregivers of children receiving oral investigational PGHD treatment (13.3%, n=2), the most often mentioned PGHD treatment impact on caregivers was added burden/responsibility (100.0%, n=2).	*Well, there's a lot of planning. We…make sure that whatever the treatment needs impacts us, not [child]. So…making sure we order the medication on time. That it arrives on a day that somebody can bring it in. That it's kept at the right temperature. That he's injected. That we remind. That we have notes that we write down. All those things, yes. It's not, it's not convenient. (mother of 11-year-old boy, injectable treatment)* *…dealing with specialty pharmacies and the…insurance is…a serious headache…and eats up a lot of time...I've gotten better at it over the years, but…it's practically a part time job sometimes. (mother of 8-year-old girl, injectable treatment)*

Table 4 Demographic and General Health Characteristics: Child Concept Elicitation Participants

Demographic Characteristics: Child Concept Elicitation Participants	Total (*n*=15)
Child age (years)[a]	
Mean(SD)	11.2 (0.7)
Range	10.1–12.8
Child gender, n(%)	
Male	11 (73.3)
Female	4 (26.7)
Child's race/ethnicity, n(%)[b]	
White	13 (86.7)
Latino or Hispanic	3 (20.0)
Asian	1 (6.7)
Prefer not to answer	1 (6.7)

(*Continued*)

Table 4 (Continued).

Health Background Characteristics: Child Concept Elicitation Participants	Total (*n*=15)
Child age (years) at GHD diagnosis	
Mean(SD)	7.4 (1.8)
Range	5–10
Child age (years) started first prescription PGHD medication	
Mean(SD)	7.5 (1.7)
Range	5–10
Current prescription PGHD treatment, n(%)	
Injectable[c]	14 (93.3)
Oral	1 (6.7)
Frequency child's current prescription PGHD medication, n(%)	
Daily	1 (6.7)
6 days/week	14 (93.3)

Notes: Percentages may not add to 100 due to rounding. [a] Child age at the time of interview ranged from 10–11 years for girls and 10–12 years for boys due to differing inclusion criteria. [b] Responses are not mutually exclusive. [c] All injectable GHD medication was administered with an injection pen.
Abbreviations: GHD, growth hormone deficiency; PGHD, pediatric growth hormone deficiency; SD, standard deviation.

Table 5 Demographic Characteristics: Caregivers of Child Concept Elicitation Participants

Demographic Characteristics: Caregivers of Child Concept Elicitation Participants	Total (*n*=15)
Caregiver age (years)	
Mean(SD)	43.3 (5.0)
Range	34–53
Caregiver relationship to child, n(%)	
Mother	10 (66.7)
Father	5 (33.3)
Caregiver race/ethnicity, n(%)[a]	
White	12 (80.0)
Latino or Hispanic	3 (20.0)
Asian	1 (6.7)
American Indian or Native Alaskan	1 (6.7)
Prefer not to answer	1 (6.7)

(*Continued*)

https://doi.org/10.2147/PPA.S500330

Table 5 (Continued).

Demographic Characteristics: Caregivers of Child Concept Elicitation Participants	Total (*n*=15)
Caregiver education, n(%)	
Vocational or technical school	1 (6.7)
Some college	1 (6.7)
College or university degree	6 (40.0)
Post-graduate degree	7 (46.7)
Caregiver primary work status, n(%)[a]	
Work full time for pay	7 (46.7)
Homemaker/caregiver	6 (40.0)
Work part time for pay	4 (26.7)
Disabled	2 (13.3)
Student	1 (6.7)
Retired	1 (6.7)
Not working	1 (6.7)

Notes: Percentages may not add to 100 due to rounding. [a]Response categories are not mutually exclusive, so percentages do not add to 100.
Abbreviations: SD, standard deviation; GHD, growth hormone deficiency; US, United States.

Child Interview Findings

Thematic saturation for the 15 child interviews identified 104 different concepts related to their GHD treatment preferences and experiences. Following the 12th interview, saturation was considered reached with 99 concepts mentioned (95.2%).

From the child interview transcripts' analysis, treatment preference and impact themes were identified. Table 6 presents a summary of findings for themes, with exemplary quotes.

Table 6 Child Interview Findings

Concept	Findings	Exemplary Quotes
Treatment likes/ dislikes	Among children treated with injectable PGHD medication (93.3%, n=14), the most frequently mentioned treatment likes were efficacy (78.6%, n=11) and general positive feelings (eg, feeling happy or confident about treatment) (42.9%, n=6). The most often mentioned treatment dislikes were the needle/ injection (64.3%, n=9) and child pain/discomfort (35.7%, n=5). For the one child (6.7%, n=1) treated with oral investigational PGHD treatment, treatment likes included the tablet form and the treatment being quick/easy to administer. No oral treatment dislikes were reported by the child participant who was currently taking oral investigational PGHD treatment.	*I think it-it's-it can sometimes be a pain in the butt, but overall…I know that it-it helped me to, you know, grow. And I'm -I'm happy that I take it and I've gotten used to it, but it's still not something…you look forward to that much. (11-year-old boy, injectable treatment)* *I don't like that it's a shot because I don't really like shots, and…I don't like, like, setting the shot up 'cause it's, like, kind of hard and annoying. (10-year-old girl, injectable treatment)* *[I liked that the pills] were very small…They weren't very hard to take…to swallow. (10-year-old boy, oral treatment)*
Treatment convenience/ ease of use	For children receiving injectable PGHD treatment (93.3%, n=14), the most often mentioned convenience/ease of use factors were the device/pen (64.3%, n=9), easy/quick administration (57.1%, n=8), and the preparation/setup (57.1%, n=8). The most frequently described inconveniences/difficulties of treatment were the time of day/schedule of dosing (57.1%, n=8) and pain/bruising at injection site (50.0%, n=7). For the child receiving oral investigational PGHD treatment (6.7%, n=1), treatment convenience/ease factors reported were easy/quick administration and tablet form. The tablets being small/easy to lose were noted as an inconvenience, and no other inconveniences were reported.	*The easiest thing about my – the medication is the shot and I think the dialing thing…so taking the shot is easy. And changing the dialing thing you think is easy. (10-year-old boy, injectable treatment)* *Sometimes, it's kind of difficult because I take it at night before I go to bed…So sometimes I want to go to – just want to go straight to bed but I have to take my shot first. (11-year-old boy, injectable treatment)*

(*Continued*)

Table 6 (Continued).

Concept	Findings	Exemplary Quotes
Treatment side effects	Among child participants taking injectable PGHD medication (93.3%, n=14), the most often mentioned treatment side effects included pain/discomfort at injection site (100.0%, n=14) and swelling/bruising at injection site (71.4%, n=10). For the child treated with oral investigational PGHD treatment (6.7%, n=1), side effects reported were increased appetite, discomfort/sensation in throat, tiredness/sleeping more, and increased energy.	*The bruises. Like, two days – for two days the injection spot hurts or aches. But my parents just tell me that it's because it's growing. (11-year-old boy, injectable treatment)* *When the needle, like, hurts sometimes. I don't really like that. (11-year-old boy, injectable treatment)* *I have a lot of bruises. And there's sometimes little red dots on where I took the injection. (10-year-old girl, injectable treatment)*
Treatment compliance	All child participants taking injectable PGHD medication (93.3%, n=14) reported missing, postponing, or changing their PGHD treatment dose in the past. The most often mentioned reasons for missing, postponing, or changing their PGHD treatment included forgetting (64.3%, n=9), time constraints/schedule (64.3%, n=9), flexibility of dosing if miss/skip or pen runs out (57.1%, n=8), and travel/being away from home (50.0%, n=7). The child treated with oral investigational PGHD treatment (6.7%, n=1) also reported missing or postponing treatment in the past. Reasons for missing/postponing treatment included forgetting, time constraints/schedule, and travel/being away from home.	*Interviewer: Mm-hmm. And what are some reasons that you may miss taking the – the growth hormone?* *Interviewee: Like…sleepovers, if we are at like a party…and then like we get home really late, and we're all really tired, so we just like will do it on Saturday. So like staying up late, sleepovers, and if like people are at our house… (12-year-old boy, injectable treatment)* *…sometimes, I–I'm at like a friend's house, or we just forget… usually, my parents just forget it. (10-year-old girl, injectable treatment)*
Treatment preferences	When questioned about what a "perfect" PGHD treatment would look like, children (n=15) most frequently indicated that it would taste good/be tasteless (46.7%, n=7), be chewable/melt in mouth (46.7%, n=7), have a flexible time of administration (40.0%, n=6), be a daily dosage with no skip days (40.0%, n=6), and have less frequent administration (40.0%, n=6). Among those receiving injectable PGHD medication (93.3%, n=14), children more frequently reported preference for a daily oral treatment (42.9%, n=6) vs a weekly injectable medication for PGHD. The most often mentioned reasons for the daily oral treatment preference were convenience (33.3%, n=2), ease of administration (33.3%, n=2), and no pain/side effects (33.3%, n=2). Fewer children expressed a preference for a weekly injectable PGHD medication (35.7%, n=5), and some children were unsure of their preference (7.1%, n=1) or indicated that their preference would depend on various factors (14.3%, n=2). The child treated with oral investigational treatment (6.7%, n=1) expressed a preference for a weekly injectable because he believed the injectable medication would be more effective than the oral form.	*…if it like tastes good…I would be like, yeah, it's time for my…pill. I am so excited… (10-year-old boy, injectable treatment)* *It would look like a gummy bear… [I would take it] Every day with my breakfast… It wouldn't be as scary, and it would come in bottles. (10-year-old girl, injectable treatment)* *[I would prefer] Taking a pill like every day…Because it's easier, and I don't like want bruises and bumps like every day…And it wouldn't be as much, like, embarrassing and stuff. (11-year-old boy, injectable treatment)*
Impacts on child's daily life	The most frequently reported PGHD treatment impacts on daily life for children treated with injectable medication (93.3%, n=14) were impacts on social activities/relationships (64.3%, n=9), evening routine/schedule (57.1%, n=8), and travel/being away from home (35.7%, n=5). The child treated with oral investigational PGHD treatment (6.7%, n=1) reported no treatment impacts on daily life.	*…if I'm playing a game with my friends, I have to like stop in the middle of the game to go up…And get [the injection treatment done]. (12-year-old boy, injectable treatment)* *…when I'm getting home from, like, a family dinner…my dad [will] just go:* "Go to the couch. We're doing the shot". *And…I want to…shower and go to bed. Like, I'm really tired, but I have to do it… so it's kind of annoying, like, just having to do it…at night, when I just want to, like, go to bed. (10-year-old girl, injectable treatment)*
Impacts on child's emotional well-being	For children treated with injectable PGHD medication (93.3%, n=14), the most often mentioned emotional feelings associated with treatment were positive (eg, happy) (71.4%, n=10), anxious/worried (64.3%, n=9), annoyed/irritated (57.1%, n=8), resistance/avoidance of treatment (57.1%, n=8), and fearful/scared (50.0%, n=7) feelings. The child treated with oral investigational treatment (6.7%, n=1) reported positive feelings about treatment and no negative emotional impacts associated with treatment.	*I think I like taking it because, like, again, I can see a difference. And it just like – if when I can see the difference it just boosts my – like – my like happiness, because like I could see it's working and stuff. (12-year-old boy, injectable treatment)* *I would say what makes me worried or anxious is screwing it up. Messing the whole thing up. [Interviewer: In terms of getting the injection in your body, or in what way?] The injection in your body, yeah. (10-year-old girl, injectable treatment)*

Questionnaire Development

Based on the analysis of the CE interview transcripts, two questionnaires were developed: the GHD-Preference Measure (GHD-PRM) and the GHD-Attribute Measure (GHD-ATM). Two versions of each of the questionnaires were generated; one to be completed by children with GHD aged ≥ 10 years to ≤ 12 years and one to be completed by the caregivers of children with GHD aged ≥ 3 years to ≤ 12 years.

The GHD-PRM was intended to be used when the respondent had experienced 2 different treatment options, whereas the GHD-ATM was designed to be relevant when a respondent had not experienced the 2 treatment options being investigated.

The items for the questionnaire were based on the major subthemes/issues identified in the analysis, using caregiver and child words as much as possible. The criteria for identifying whether concepts were considered major included:

- Endorsement percentages of at least 10% by both child and caregiver participants,
- The concept had to be applicable without respect to treatment type, and
- The concept had to be applicable to subjects participating in a clinical trial.

First, the GHD-PRM, which asks the respondents to indicate their preference for one of two different treatments that they have experienced and to identify the attributes which underpin their preference, was generated. The GHD-PRM assesses: 1) which treatment is preferred; 2) factors that affected their treatment preference; 3) selection of the most important factor (child version) or a ranking of three most important factors (caregiver version) for the treatment preferred; 4) which treatment they would prefer to continue after clinical trial completion; and 5) which treatment they would recommend to others. The caregiver version has two additional stems with items asking for the caregiver's personal experience with their child's GH medication.

The GHD-ATM was developed after the GHD-PRM. This questionnaire leveraged what was learned from the interviews in terms of what were the major attributes underpinning the choice/preference for a treatment by mirroring the attributes of the GHD-PRM, but rather than asking the respondent to make any comparisons, the respondent is asked to simply rate the degree or "presence" of each attribute in their current treatment. The attribute questionnaire contains a 5-point, Likert-type response scale. Items measuring ease/difficulty had response scales ranging from "Not at all easy" to "Extremely easy". Items measuring like/dislike had response scales ranging from "Not at all" to "Extremely". Items measuring "how often" had response scales ranging from "Never" to "Always".

The GHD-PRM is intended to be used in study designs such as a cross-over or switch study when a respondent has had the opportunity to experience different treatments, whereas the GHD-ATM is intended to be used in designs such as a clinical trial or in clinical practice when the respondent has not experienced a comparator treatment.

These questionnaires are meant to be completed as self-reported questionnaires, except the caregiver versions, which include two items asking about the child's emotional state. These questions were considered as observer-reported outcome (ObsRO) questions and included instructions to complete the items based upon what the caregiver had seen or been told, and not on their opinion. These items have an additional response option for "Don't know" to allow caregivers to indicate when they do not have enough information based on their observations to answer the item.

Cognitive Debriefing Assessment Results

Translatability assessment identified only minor formatting and wording issues which were incorporated into the draft questionnaires used for the cognitive debriefing assessment interviews. The debriefing assessment interviews were conducted in an independent sample of 22 respondents (12 caregivers, 10 children). Four blocks of caregivers and three blocks of children were needed to refine the questionnaires, items, and instructions in terms of comprehension, formatting, readability, and relevance.

Final Measures

The child version of the GHD-PRM has 20 items, and the caregiver version has 31 items. Both versions share 20 conceptually equivalent items. Examples of shared items from the GHD-PRM child version are shown in Figure 2.

Ten additional items in the caregiver version ask questions about the caregiver and why they prefer the GH medication they selected. Figure 3 presents examples of these items. One additional question asks the caregiver to rank the three most important reasons they prefer the medication they chose.

Both versions of the GHD-ATM have 16 items, which are conceptually equivalent, asked from either the child or caregiver perspective. Examples of items from the GHD-ATM are shown in Figure 4.

The following questions are about your experiences with your two different growth hormone study medicines and which medicine you like more.

Instructions:

- Please read each question carefully.
- There are no "right" or "wrong" answers. THIS IS NOT A TEST.

Q.1 Which growth hormone medicine do you like more?

Please check only one box.

<<Insert "Medication 1">>	❑
<<Insert "Medication 2">>	❑
I like them both the same. ----------> Please SKIP to Question 4.	❑

Q.2 Please think about why you like the growth hormone medicine (the one you chose in Question 1) more than the one you did not choose.

For each of the following questions, check "Yes" if it is a reason why you like this medicine more. If it is not a reason why you like the medicine more, or you are not sure, please check "No".

Please make sure you answer every question.

I like this medicine more because it is:	*Yes*	*No*
a. Easier to store (keep at the right temperature)	❑	❑
b. Easier to prepare	❑	❑
c. Easier to know how much of the medicine to take	❑	❑

Figure 2 Examples of shared items from the GHD-PRM Child version.

I prefer this medication because:	*Yes*	*No*
a. I am less stressed about the medication	❑	❑
b. I am less afraid to give the medication	❑	❑

Figure 3 Example items asked of caregivers regarding themselves about their treatment preference from the GHD-PRM Caregiver version.

How easy or hard is it to:	*Not at all easy*	*A little easy*	*Somewhat easy*	*Very easy*	*Extremely easy*
a. Store the medicine (keep at the right temperature)?	❑	❑	❑	❑	❑
b. Prepare the medicine?	❑	❑	❑	❑	❑
c. Know how much medicine to take?	❑	❑	❑	❑	❑

Figure 4 Example items from the GHD-ATM Child version.

Scoring

The GHD-PRM can be scored and/or interpreted in 3 different ways:

1. Simple count of the stated preference of which treatment is preferred for the sample under study. For example, x number of people prefer treatment Y over treatment Z.
2. Summary count of the number of attributes for the preferred treatment as an indication of the strength of the preference for the preferred treatment. For example, there are x number of attributes (explanations for) why treatment Y is preferred over treatment Z.
3. Rank ordering of the individual attributes of the preferred treatment to better understand the "why" of treatment preference.

https://doi.org/10.2147/PPA.S500330

The GHD-ATM is scored as one total transformed score with reverse coding as needed so that a higher score indicates a stronger positive treatment attribute presence.

Discussion

Although there is FDA guidance on the importance of PED and PPI evidence, as well as proposed guidelines and frameworks on how to use and evaluate this type of data,[12,24,25] the actual methodology to develop assessments, apart from conjoint analysis experiments, is less common. The processes used to develop these novel PGHD treatment preference and attribute questionnaires, which do not require the patient to perform a complex risk/benefit analysis regarding their preferences, are meant to help fill that gap. The novel measures fall under the category of a clinical outcome assessment but are not strictly speaking a PRO questionnaire as they assess preferences regarding treatment attributes rather than outcomes. Further, PRO questionnaires may provide a snapshot of a patient's own assessment of various outcomes at a given point in time; however, they do not convey how much the patient values one specified outcome or therapy when compared to other potential outcomes and therapies.[3] Nor would they be considered an ObsRO questionnaire when the patient is a child and the caregiver is completing the questionnaire; as it is most often the caregiver's preference, even if based on the child's experience, that would be most appropriate to assess. By drawing from best practices for developing PRO and ObsRO measures, treatment preference and attribute measures can be developed with scientific rigor and validity. Further, combining methodology drawn from PRO/ObsRO measure development and discrete choice concepts allows these questionnaires to be relevant to all aspects of drug development as well as clinical practice and research as they go beyond the simple "which do you prefer" and assess the "why" by understanding the attributes which underpin a preference as revealed (actual) rather than stated (hypothetical). Lastly, these measures are practical to develop and easily interpretable, which should allow the research community to actively embrace them. By basing the development of preference and attribute questionnaires on a range of best practices across available methodologies, we can ensure that these patient-centric questionnaires provide credible and meaningful evidence when evaluating treatment options. Although GHD is used here as the disease model for the development of these measures, we believe this methodology is applicable across disease states and can serve as a prototype for future preference and attribute tool development.

Preference questionnaires present their own unique set of methodological challenges for development and interpretation, especially when the treatment is for a child, yet it is the caregiver who is the decision maker for preferences. In this case, some preferences may be experienced by the caregiver while others may be based on how the child feels or reacts. By incorporating best practices for both PRO and ObsRO measures' development, we believe the methodology exists to meet this challenge by clearly delineating which preferences are caregiver based and thus, a caregiver is able to assess regarding their own experience or using best practices for ObsRO measure development to report on child experiences. By providing clear instructions to the caregiver to only select the response that best matches what they have seen or been told by their child as well as including a "Do not know" response option, this challenge can be addressed.

Assessing preference is not a marketing message or simply a question of, "Which drug do you prefer?" but rather also, an understanding of why one drug is preferred over another and the strength of that preference. Treatment preference questionnaires, when used in a trial such as a short-term cross-over design which would limit recall bias or with an extension arm where patients on treatment A are given the chance to continue on treatment B, can provide real-world evidence of preferences if the assessments are done within a reasonable time frame of the switch. However, their utility may be limited when a patient has not had the opportunity to experience more than one treatment option on which to base their preference and can only provide hypothetical preferences. This is the case in a treatment efficacy trial where patients are randomized to either treatment A or B but do not experience both. In this situation, we propose that the scientific evidence used for the development of a preference "choice" questionnaire can be leveraged by using the data to also develop a treatment attribute questionnaire. The attribute questionnaire does not ask for a comparison between treatments but rather asks the respondent to rate the presence or strength of the attributes which underly preference and are key factors contributing to preference choices. An attribute questionnaire of this type makes it possible to provide evidence that drug A (experienced by one treatment arm) has more or less of the necessary attributes which would suggest that the respondent would prefer the treatment. By basing the preference and attribute questionnaires'

development on best practices of PRO and ObsRO measures' development, we can ensure that these questionnaires provide credible and meaningful evidence when evaluating treatment options.

Scoring is another methodological challenge as a preference questionnaire does not necessarily contain "domains" or clusters of concepts and as such is scored as a simple count of number of preferred attributes that make up a preference for one drug versus another. However, it should be noted that, as reported by clinicians and caregivers, efficacy and safety are generally the key drivers of preference. The simple count of number of attributes is unweighted for these key preferences and thus, when using the measure, the interpreter may wish to examine attributes with or without these key attributes depending upon the question being examined. For example, if the question is, "What attributes beyond safety and efficacy are important?" then a score without these attributes may be preferred.

Standard of care therapy for PGHD with daily SQ injections poses challenges in terms of treatment burden, satisfaction, and adherence. Non-adherence with daily GH therapy is common. Kaplowitz et al[26] reported suboptimal adherence rates, with only 32% of commercial and 18% of Medicaid patients reporting rates exceeding 80%. In a national study of GH adherence in New Zealand children,[27] two-thirds of patients missed more than one dose per week. Predictably, with greater non-adherence there was a progressive decline in annualized height velocity (growth). Despite years of treatment with daily GH, the full genetic height potential may not be reached, as reported in a meta-analysis of registry data of >4,500 patients.[28] The current landscape of PGHD treatment includes traditional daily GH injections, recently approved once-weekly long-acting GH injections, and an investigational oral secretagogue in clinical trials. Clinical tools such as PPI can aid in shared decision making between the provider and the caregiver/child to help optimize treatment success.

Limitations

It should be noted that respondents for the CE interviews came from a variety of sources, including the general population of children with GHD as well as from those participating in a clinical trial, and there was wide variation in some respondent characteristics. Although this heterogeneity of respondents provides greater generalizability of findings and a broader range of experiences,[29] it should be taken into consideration when interpreting findings. Additionally, this study was based in the US. Consequently, there may be cultural factors relevant for other countries that were not adequately captured.

Development of the preference attributes based on interviews with patients who may not have experienced all available treatment options, as was the case in this study, poses an additional challenge. Unfortunately, the oral treatment sample was small due to the reality that there are no oral treatments currently available outside the clinical trial setting. Therefore, it was not possible to assess saturation of concepts by treatment type. However, the sample size, when combining those on both injectables and oral treatments was adequate for capturing broad treatment experiences,[30,31] and 95% saturation of relevant concepts was achieved. It would be valuable to further study experiences with oral GH treatments once they are more readily available. When all treatment options are not available, hypothetical scenarios for CE interviews and the CD assessments can be considered. Lastly, larger quantitative studies, incorporating these questionnaires as outcome measures, may also provide the opportunity to psychometrically examine some of their measurement characteristics and structure, such as inter-item correlations and test-retest reliability.

Currently, there are limited disease-specific preference measures for GHD treatment. The GHD-PRM and GHD-ATM could prove to be valuable assets in evaluating and comparing factors influencing patients' treatment satisfaction across diverse settings, administration routes and mechanisms of action, including newer routes of administration such as oral. By actively participating in the dimensions of patient care captured by the GHD-PRM and GHD-ATM, the importance of understanding patient preferences in the clinical setting can be reinforced. This understanding holds the potential to improve treatment compliance, enhance the social and emotional well-being of children with PGHD and their caregivers, and positively impact clinical outcomes. Additionally, greater understanding of these factors among clinicians will facilitate health care provider–patient communication and help clinicians better tailor treatment plans to patients' needs. Lastly, the ability of regulatory, payer and clinical audiences to better understand the patient experience should not be underestimated.

Conclusion

In summary, the GHD-PRM and the GHD-ATM can be considered rigorously developed and valid preference and attribute questionnaires specific to PGHD and other conditions treated with recombinant human GH injections. These preference and attribute measures can be incorporated into clinical trials and clinical practice and may also inform future research regarding the assessment of treatment preferences in other conditions.

Abbreviations

CD, cognitive debriefing assessment; CE, concept elicitation; FDA, United States Food and Drug Administration; GHD-ATM, Growth Hormone Deficiency-Attribute Measure; GHD-PRM, Growth Hormone Deficiency -Preference Measure; GH, growth hormone; GHD, growth hormone deficiency; ICH, International Council on Harmonization; IRB, Independent Review Board; ObsRO, observer-reported outcome; PED, patient experience data; PGHD pediatric growth hormone deficiency; PPI, patient preference information; PRO, patient-reported outcome; SD, standard deviation; SQ, subcutaneous; US, United States.

Data Sharing Statement

The datasets used and/or analyzed for the research presented in the publication may be available on a case-by-case basis for reasonable requests from the corresponding author.

Ethics Approval and Informed Consent

Independent Review Board (IRB) approval for study protocol LP22-PGHDPrefQ (IRB Tracking Number: 20230357) was received from WCG IRB. Informed consent was obtained from all study participants.

Acknowledgments

The authors would like to thank the study participants for sharing their experiences and for their valuable feedback.

The abstract of this paper was presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference, 2024, as a poster presentation with interim findings. The poster's abstract was published in "ISPOR Abstracts 2024" in *Value in Health*: DOI: 10.1016/j.jval.2024.03.2130.

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 Lumos Pharma, Inc.

Disclosure

MB, KMP, SLA, and JFB are consultants to the pharmaceutical industry, including Lumos Pharma, Inc. MM, AB, and PP are full-time employees of Lumos Pharma, Inc. AM is a Principal Investigator with Ascendis, The Brod Group, Novo Nordisk, Pfizer, and OPKO. The authors report no other conflicts of interest in this work.

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