Assessing Treatment Preference in Pediatric Growth Hormone Deficiency: Challenges and Proposed Solutions

PCR252

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BACKGROUND

- Patient Experience Data (PED) capturing the patient voice, is gaining increasing recognition as having the potential to provide evidence across the drug development continuum and for use in risk/benefit analysis to evaluate new drugs and inform reimbursement and pricing decisions.
- PED is intended to provide information about patients' experiences with a disease, treatment, or condition and includes the experiences, perspectives, needs, and priorities of patients (Title III, Section 3002(c) of the 21st Century Cures Act) [1].
  - The United States (US) Food and Drug Administration (FDA) position on the importance of PED is echoed by the European Medicines Agency [2].
- One type of PED regards patient preference information (PPI) for one drug or treatment over another due to factors such as efficacy, side effects, and impacts on daily life and functioning.
  - PPI is defined as qualitative or quantitative assessments of the relative desirability (what is valued most) or acceptability (perspective on risk and benefit) to patients and care-partners (e.g., caregivers) of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions [3].
- Assessing preferences is not simply the 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.
- Methodologies for assessing preference can be either qualitative or quantitative ranging from focus groups to discrete choice experiments with up to 32 different methodologies identified [4, 5].
- Treatment preference questionnaires, in a trial such as a cross-over design 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.
  - 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.

OBJECTIVES

- The purpose of this poster is to suggest a process for developing easily administered and interpretable preference questionnaires, using growth hormone treatment for children, which can be used in scenarios when respondents have experienced multiple treatment options or when only one treatment has been experienced.
  - This process draws from aspects of best practices for the development of patient-reported outcome (PRO) measures [6] as well as the underlying concept of attributes on which preferences are based used in discrete choice methodologies.

METHODS

- Methodology for establishing content validity included literature review and concept elicitation interviews with clinical experts, caregivers of children with growth hormone deficiency (GHD), and children with GHD.
  - The interview guide elicited information regarding attributes of treatment that were preferred (or liked vs. not) in terms of:
    - the 3 pillars of treatment satisfaction: convenience, efficacy, and side effects [7]; and
    - interference in daily life, emotional well-being, and compliance.
- Two questionnaires were developed based on adapted grounded theory qualitative analysis of the concept elicitation interviews:
  - A treatment preference questionnaire, (GHD-Preference Measure) and a treatment attribute questionnaire (GHD-Attribute Measure).
    - The preference questionnaire was intended to be used in scenarios when the respondent had experienced 2 different treatments options.
    - The attribute questionnaire was designed to be relevant in scenarios where a respondent had not had the opportunity to experience both treatment options.
  - Two versions of each of the questionnaires were generated: one for children with GHD age ≥ 10 to ≤ 12 years and one for the caregiver of children with GHD age ≥ 3 to ≤ 12 years.

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RESULTS

Sample Description: Caregiver and Child Interview Participants

Table 1 presents the demographic characteristics of caregiver participants and the demographic and general health characteristics of their children with GHD, as well as the demographic and general health characteristics of child participants as reported by their caregivers.

Table 1. Demographic and General Health 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 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)
Child's age (years)	
Mean(SD)	8.4 (2.6)
Range	4.3-11.6
Child's gender, n(%)	
Male	9 (60.0)
Female	6 (40.0)
Child's age (years) started first prescription GHD medication	
Mean(SD)	5.7 (2.4)
Range	1.4-10.0
Child's current prescription GHD treatment, n(%)	
Injectable[b]	13 (86.7)
Oral	2 (13.3)
Frequency of child's current prescription GHD medication, n(%)	
Daily	3 (20.0)
6 days/week	11 (73.3)
Weekly	1 (6.7)
CHILD Concept Elicitation Participants	**Total (*n*=15)**
Child's age (years)[c]	
Mean(SD)	11.2 (0.7)
Range	10.1-12.8
Child's gender, n(%)	
Male	11 (73.3)
Female	4 (26.7)
Child's race/ethnicity, n(%)[a]	
White	13 (86.7)
Latino or Hispanic	3 (20.0)
Asian	1 (6.7)
Prefer not to answer	1 (6.7)
Child's age (years) started first prescription GHD medication	
Mean(SD)	7.5 (1.7)
Range	5-10
Child's current prescription GHD treatment, n(%)	
Injectable[b]	14 (93.3)
Oral	1 (6.7)
Frequency of child's current prescription GHD medication, n(%)	
Daily	1 (6.7)
6 days/week	14 (93.3)

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

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Caregiver Interview Findings

Key findings reported by **at least 40.0%** of the 15 caregivers of children with GHD receiving injectable GHD treatment (n=13, n=86.7%) or oral GHD medication (n=2, 13.3%) are shown in Table 2.

Table 2. Caregiver Interview Findings

CONCEPT	*KEY FINDINGS*		
Treatment likes and dislikes	*Injectable*	*Likes* ⇨	device/pen (53.8%, n=7); ease of preparation/setup (46.2%, n=6)
		Dislikes ⇨	needle/injection (46.2%, n=6)
	Oral	*Likes* ⇨	tablet form (100.0%, n=2); no injections (100.0%, n=2); no child complaints (50.0%, n=1); time of day/schedule (50.0%, n=1); flexible administration time (50.0%, n=1); quick/easy administration (50.0%, n=1)
		Dislikes ⇨	insufficient tablet coating (50.0%, n=1)
Treatment convenience and ease of use	*Overall*	*Importance* ⇨	over half indicated convenience (60.0%, n=9) was important or very important in their satisfaction with their child's GHD treatment
	Injectable	*Convenience* ⇨	device/pen (69.2%, n=9); time of day/schedule of dosing (61.5%, n=8); adjusting/calculating doses (61.5%, n=8); preparation/setup (53.8%, n=7)
		Inconvenience ⇨	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); drug/device availability/access (61.5%, n=8)
	Oral	*Convenience* ⇨	time of day/schedule of dosing (100.0%, n=2); packaging (100.0%, n=2); storage/refrigeration requirements (100.0%, n=2); tablet form (100.0%, n=2)
		Inconvenience ⇨	travel/being away from home (50.0%, n=1); doctor appointments/tests (50.0%, n=1)
Treatment side effects	*Overall*	*Importance* ⇨	most reported that side effects (80.0%, n=12) were important or very important in their satisfaction with their child's GHD treatment
	Injectable	*Most reported* ⇨	pain/discomfort at injection site (69.2%, n=9)
	Oral	*Most reported* ⇨	increased appetite (50.0%, n=1)
Treatment compliance	*Overall*	*Compliance* ⇨	most (n=14, 93.3%) reported missing, postponing, or changing their child's GHD treatment in the past
	Injectable	*Key reasons* ⇨	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); time constraints/schedule (69.2%, n=9)
	Oral	*Key reasons* ⇨	flexibility of dosing if miss/skip a dose (50.0%, n=1); forgetting (50.0%, n=1)
Impacts on child's daily life	*Injectable*	*Key impacts* ⇨	impact on travel/being away from home (92.3%, n=12); impact on social activities/relationships (46.2%, n=6)
	Oral	*Key impacts* ⇨	impact on schedule/routine (50.0%, n=1); impact on school/camp (50.0%, n=1)
Impacts on child's emotional well-being	*Injectable*	*Key impacts* ⇨	feeling anxious/worried (69.2%, n=9); acceptance/being "used to" treatment (69.2%, n=9); resisting/avoiding treatment (61.5%, n=8); positive feelings about treatment (53.8%, n=7); feeling sad/crying (53.8%, n=7); hate/dislike of treatment (46.2%, n=6)
	Oral	*Key impacts* ⇨	positive feelings about treatment (100.0%, n=2); feeling anxious/worried (50.0%, n=1); acceptance/being "used to" treatment (50.0%, n=1); resisting/avoiding treatment (50.0%, n=1)
Impacts on caregivers	*Injectable*	*Key impacts* ⇨	added burden/responsibility (92.3%, n=12)
	Oral	*Key impacts* ⇨	added burden/responsibility (100.0%, n=2)
Treatment efficacy	*Overall*	*Importance* ⇨	all (100.0%, n=15) indicated that treatment efficacy was important or very important in determining their satisfaction with their child's treatment
	Overall	*Most often considered factors* ⇨	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); child's emotional well-being (40.0%; n=6)
Treatment preferences	*Overall*	*Most important drug features* ⇨	treatment efficacy (66.7%, n=10); tablet form (60.0%, n=9); less frequent administration (46.7%, n=7); quick/easy to administer (46.7%, n=7); no/little side effects (40.0%, n=6); not needing refrigeration (40.0%, n=6)
	Overall	*Which prefer?* ⇨	treatment that stimulates child's growth hormone production (66.7%, n=10) vs. treatment that replaces child's growth hormone (6.7%, n=1)
	Overall	*Which prefer?* ⇨	daily oral (53.3%, n=8) vs. weekly injectable (33.3%, n=5)

Child Interview Findings

Key findings reported by **at least 40.0%** of the 15 children with GHD receiving injectable GHD treatment (n=14, n=93.3%) or oral GHD medication (n=1, 6.7%) are shown in Table 3.

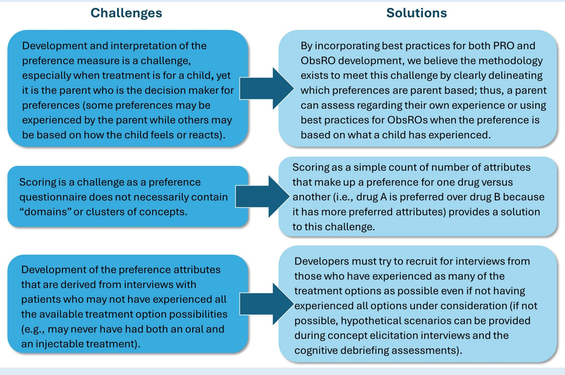
Table 3. Child Interview Findings

CONCEPT	*KEY FINDINGS*		
Treatment likes and dislikes	*Injectable*	*Likes* ⇨	efficacy (78.6%, n=11); general positive feelings (e.g., feeling happy or confident about treatment) (42.9%, n=6)
		Dislikes ⇨	needle/injection (64.3%, n=9)
	Oral	*Likes* ⇨	tablet form (100%, n=1); treatment quick/easy to administer (100%, n=1)
		Dislikes ⇨	None
Treatment convenience and ease of use	*Injectable*	*Convenience* ⇨	device/pen (64.3%, n=9), easy/quick administration (57.1%, n=8), preparation/setup (57.1%, n=8); time of day/schedule of dosing (50.0%, n=7)
		Inconvenience ⇨	time of day/schedule of dosing (57.1%, n=8); pain/bruising at injection site (50.0%, n=7)
	Oral	*Convenience* ⇨	easy/quick administration and tablet form (100%, n=1)
		Inconvenience ⇨	tablets being small/easy to lose (100%, n=1)
Treatment side effects	*Injectable*	*Most reported* ⇨	pain/discomfort at injection site (100.0%, n=14); swelling/bruising at injection site (71.4%, n=10)
	Oral	*Most reported* ⇨	increased appetite, discomfort/sensation in throat, tiredness/sleeping more, and increased energy (100%,n=1)
Treatment compliance	*Overall*	*Compliance* ⇨	all (100.0%, n=15) reported missing, postponing, or changing their GHD treatment dose in the past
	Injectable	*Key reasons* ⇨	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); travel/being away from home (50.0%, n=7)
	Oral	*Key reasons* ⇨	forgetting, time constraints/schedule, and travel/being away from home (100%,n=1)
Impacts on child's daily life	*Injectable*	*Key impacts* ⇨	impact on social activities/relationships (64.3%, n=9); impact on evening routine/schedule (57.1%, n=8)
	Oral	*Key impacts* ⇨	none
Impacts on child's emotional well-being	*Injectable*	*Key impacts* ⇨	positive feelings about treatment (71.4%, n=10); feeling anxious/worried (64.3%, n=9); feeling annoyed/irritated (57.1%, n=8); resistance/avoidance of treatment (57.1%, n=8); feeling fearful/scared (50.0%, n=7); acceptance/being "used to" treatment (42.9%, n=6)
	Oral	*Key impacts* ⇨	positive feelings about treatment (100.0%, n=1)
Treatment preferences	*Overall*	*Most important drug features* ⇨	taste good/be tasteless (46.7%, n=7); be chewable/melt in mouth (46.7%, n=7); have flexible time of administration (40.0%, n=6); be daily dosage with no skip days (40.0%, n=6); have less frequent administration (40.0%, n=6)
	Overall	*Which prefer ?* ⇨	daily oral (40.0%, n=6) vs. weekly injectable (40.0%, n=6) *[child on daily oral preferred weekly injectable believing it would be more effective than oral]*

Questionnaire Development

- Preference items for the questionnaire for each major subtheme/issue were generated 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 for children (and their caregivers) in the general GHD population without respect to treatment type; and
  - the concept had to be applicable to subjects participating (and their caregivers) in a clinical trial.
- First, the GHD-Preference Measure was generated which asks the respondent to choose which of 2 different treatments that they have experienced they prefer and identify the attributes which underpin that preference.
  - The GHD-Preference Measure assesses: 1) which treatment is preferred, 2) factors chosen as to why treatment preferred, 3) selection of most important factor (child version) or rank the 3 most important factors (caregiver version) for the treatment preferred, 4) which treatment to continue taking after completion of clinical trial, and 5) which treatment recommended to others.
  - The caregiver version has 2 additional stems with items asking for the caregiver's personal experience with their child's growth hormone medication and to rank of 3 most important personal factors for the treatment preferred.
- Following the GHD-Preference Measure, the GHD-Attribute Measure was developed.
  - This questionnaire leveraged what was learned from the interviews in terms of what were the major attributes underpinning the choice/preference for treatment. HOWEVER, the respondent is not asked to make any comparisons. RATHER, the respondent is asked to rate the degree or "presence" of each attribute in their current treatment.
  - These questionnaires are meant to be completed as self-reported questionnaires, except for the caregiver version which includes 2 items asking about the child.
    - The 2 questions about the child 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; they have an additional response option, "Don't know", to allow caregivers to indicate when they did not have enough information based on their observations to answer the item.
- Cognitive debriefing found items and instructions to be comprehensive, relevant, and clear.

Figure 1. Methodological Challenges and Solutions to Developing PPI Measures



Scoring

The preference questionnaire can be scored in 3 different ways:

1. The stated preference of which treatment is preferred and/or recommended for others.
2. A summary count of the number of attributes for the preferred treatment as an indication of the strength of the preference.
3. Individual examination of the attributes of the preferred treatment in order to better understand the "why" of treatment preference.

The attribute questionnaire can be scored as one total score with reverse coding as needed so that a higher score indicates a stronger, positive treatment attribute presence and transformed scores (based on the average raw scores translated to a 0-100 scale).

CONCLUSIONS

- These measures are intended for research as well as clinical use.
  - The GHD-Preference Measure 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.
  - The GHD-Attribute Measure 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.