

# Assessing Disease and Treatment Burden for Young Children with Growth Hormone Deficiency (GHD)

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## Background

- Children with GHD, in addition to short stature, may experience physiological symptoms<sup>1</sup> as well as social and emotional problems.<sup>2</sup>
- Assessing these impacts is critical for understanding the extent of GHD disease and treatment burden and assessing treatment benefit.
- Unfortunately, no adequately designed measures exist to assess these impacts in children who are unable to answer for themselves or complete assessments designed for adults.
- Further, for the assessment of outcomes in young children (approximately age <8 years), proxy measures are not acceptable as they are not objective and/or may reflect the bias of the person acting as proxy.<sup>3,4</sup>
- Thus, a scientifically valid parent observer-reported outcome (ObsRO) measure is needed, which can provide an objective assessment of these impacts for young children.

## Objectives

- Develop a simple, scientifically valid methodology to elicit objective, ObsRO information, which could be used when developing outcome assessment measures for children too young to complete a patient-reported outcome (PRO) measure.
- Determine if this methodology allows parents of young children with GHD to objectively assess GHD disease and treatment burden experienced by their child, and mirrors child reports of these burdens.
- Develop child appropriate PROs to assess GHD disease and treatment burden.
- Develop ObsRO versions of the measures, which can be objectively completed by a parent of a young child who is unable to report for themselves.

## Methods

- A methodology to collect objective, observer-reported information regarding GHD disease and treatment burden for young children was developed.
- In order to assess the feasibility of the methodology, concept elicitation (CE) interviews with GHD children ages 8 to <13 years (pre-pubertal) and parents of children with GHD ages 4 to <13 years (pre-pubertal) were conducted.
- Based on these CE interviews, child PRO and parent ObsRO measures were generated.
- Cognitive debriefing interviews (CD) to assess comprehension, relevance, and acceptability of the measures for both parents and children were conducted.

## Results

- A methodology to elicit valid, ObsRO data from parents was designed and included:
  - Conducting focus group or telephone interviews with parents of children with GHD and children with GHD.
    - Explaining to parents that the purpose of their interview was "to provide information related to your child; specifically your observations of events and behaviours related to the impact of GHD and its treatment".
    - Instructing parents to describe only observable behaviours and specify how they knew and/or what they saw or heard to support their comments.
- Seventy CE interviews were conducted with GHD children (n=39) (Table 1a) and 31 parents of GHD children - 3 parents were interviewed about 2 of their GHD children resulting in a sample of n=34 (Table 1b).
- The interviews showed that parents were able to provide concrete examples of what they had seen or heard, which mirrored the children's experiences of reported impacts (Tables 2a and 2b).
- Based on the qualitative analysis of these interviews, 2 draft measures were developed, which underwent CD with 13 children ages 8 to <13 years and 13 parents of children with GHD ages 4 to <13 years.
  - CD resulted in a 33-item disease burden measure named Treatment Related Impact Measure - Child Growth Hormone Deficiency (TRIM-CGHD) and a 17-item treatment burden measure named Treatment Burden Measure - Child Growth Hormone Deficiency (TB-CGHD), each with a PRO and an ObsRO version.
    - The TRIM-CGHD has 4 domains: Symptoms, Physical Functioning, Social Well-being, and Emotional Well-being.
    - The TB-CGHD has 3 child-related domains: Child Physical, Child Emotional, and Child Interference.
  - CD results found that children age ≤8 years had substantially more comprehension issues understanding the intended meaning of items, had more variability in how they interpreted the recall period, and were less able and reported more nervousness when completing the measures.
    - This led to the decision that a parent-reported, ObsRO measure would be appropriate for children age <9 years.
- The PRO and ObsRO measures assess equivalent concepts, each with their own parent or child appropriate instructions, language, and formatting (Figure 1).
  - Child PRO versions contain brief, straightforward instructions; the items are brief, simple, and in language used by the children in the CE and CD interviews; instructions let the child know that they will not be "graded" on their responses and that their answers will not be shared with others; and simple clip art - offering a visual cue to what the items in a section relate to - are also shown.
  - Parent ObsRO versions include instructions emphasising that they MUST base responses ONLY on what they have observed or heard about their child or others about their child and NOT on what they think; an option for "Don't Know" is provided for each item in the event that the parent has no 'evidence' (observable information) on which to base their answer.

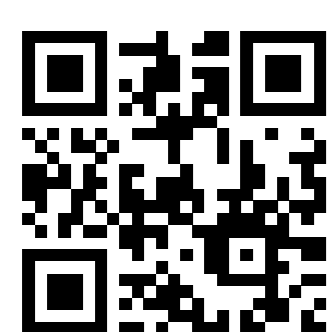
Table 1a Child Sample Description

Demographic Characteristics		Germany n=11	UK n=7	US n=21	Total n=39
Age	8-9 yrs	n (%) 4 (36.36)	1 (14.28)	2 (9.52)	7 (17.94)
	10-12 yrs	n (%) 7 (63.63)	6 (85.71)	19 (90.47)	32 (82.05)
Gender	Female	n (%) 5 (45.45)	2 (28.57)	4 (19.04)	11 (28.20)
	Male	n (%) 6 (54.54)	5 (71.42)	17 (80.95)	28 (71.79)
Ethnicity	White	n (%) —	5 (71.42)	19 (90.47)	24 (61.53)
	Persian	n (%) —	1 (14.28)	—	1 (2.56)
	Asian	n (%) —	1 (14.28)	—	1 (2.56)
	Other	n (%) —	—	2 (9.52)	2 (5.12)
	N/A	n (%) 11 (100.00)	—	—	11 (28.20)
Other Prescription Medications	Yes	n (%) 4 (10.25)	1 (2.56)	11 (28.20)	16 (41.01)
Age (yrs) at Diagnosis	Mean (Range)	4.72 (3-8)	9.42 (3-12)	10.09 (3-12)	8.07 (3-12)
Ever taken GHD medications	Yes	n (%) 11 (28.20)	7 (17.94)	18 (46.15)	36 (92.29)
Age (yrs) initiated GHD medication	Mean (Range)	5.18 (4-8)	10.28 (8-12)	10.27 (3-12)	8.57 (3-12)

Table 1b Parent Sample Description

Demographic Characteristics		Germany n=10	UK n=5	US n=19	Total n=34
Age of child	< 8 yrs	n (%) 6 (60.00)	4 (80.00)	4 (21.05)	14 (41.18)
	8-9 yrs	n (%) 4 (40.00)	1 (20.00)	3 (15.78)	8 (23.53)
	10-12 yrs	n (%) —	—	12 (63.15)	12 (35.29)
Gender of child	Female	n (%) 3 (30.00)	2 (40.00)	6 (31.57)	11 (32.35)
	Male	n (%) 7 (70.00)	3 (60.00)	13 (68.42)	23 (67.64)
Relationship to child	Mother	n (%) 7 (70.00)	5 (100.00)	18 (94.73)	30 (88.23)
	Father	n (%) 3 (30.00)	—	1 (5.26)	4 (11.76)
Parent age	Mean (Range)	39.6 (33-47)	37.2 (23-48)	40.47 (26-47)	39.09 (23-47)
Parent marital status	Single	n (%) —	—	1 (5.26)	1 (2.94)
	Married	n (%) 6 (60.00)	2 (40.00)	17 (89.47)	25 (73.52)
	Partnered	n (%) 1 (10.00)	3 (60.00)	1 (5.26)	5 (14.70)
	Divorced	n (%) 3 (30.00)	—	—	3 (8.82)
	N/A	n (%) 10 (100.00)	—	2 (10.52)	2 (5.88)
Child age (yrs) at Diagnosis	Mean (Range)	4.4 (3-7)	4.6 (3-6)	8.63 (3-12)	5.88 (3-12)
Child ever taken GHD medications	Yes	n (%) 9 (90.00)	4 (80.00)	16 (84.21)	29 (85.29)
Child age (yrs) initiated GHD medication	Mean (Range)	4.55* (4-6)	5.5* (4-8)	8.67* (3-12)	6.24 (3-12)

\* The mean reflects the response of 9 German, 4 UK, and 17 US participants. The responses not included were "N/A".



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Table 2a Examples of Aligned Child PRO and Parent ObsRO Quotes for the TRIM-CGHD

Domain	Item	Child Self-Report	Parent-Reported Observation
Physical	<b>In the past week:</b>		
	How tired were you during the day?	Jeffery: [Before treatment] I just like, sometimes just can't stay awake. I get really tired sometimes.	Michelle: She doesn't like playing the running games... There's a bit of reluctance with some stuff, she'll say 'I don't want to, I'm tired'.
	How much appetite did you have (how much and how often you eat)?	Justin: I'm eating more. I used to not be eating all of my plate, but now I'm eating most of it.	Brittany: She was really under with her calories and now she'll eat two snacks, and she'll eat all three meals. It's a pretty dramatic increase.
Social	<b>In the past week, because of your size, how often:</b>		
	Did people think you were younger than you are?	Jacob: Well, yeah. I - - the first time I started doing them, I was like 10 or 11; and before then, everyone always thought I was some 8-year-old or something like that.	Kim: No, just the biggest one is wanting to be - - look like the oldest, because I get a lot of people that do say, "Oh, are they the same age?"
	Were you left out of sports or playing with other kids?	Marco: I was one of the shortest in my grade and it was pretty rough because I like sports and I worked hard at them, but it was hard to do good at them because all the kids were bigger than me.	Rita: When we went on holidays with several families, all were in the pool, but our son had to get out of the pool after three minutes, because he was exhausted.
Emotional	<b>In the past week, because of your size, how often did you feel:</b>		
	Angry?	Julia: I feel kind of sad and mad my body doesn't work right, but I'm kind of happy that I can grow more than I would have if I didn't do it.	Kelly: Yeah, even last summer. There was still one ride he couldn't ride. And we didn't even talk about it. He would get so mad.
	Upset?	Andi: It gets on my nerves when people say that I am so small.	Maggie: Like she sings like in the restaurant, like she's singing some pop song or whatever, my daughter, in like Arby's and these women are like: "Look, she sings. Isn't she such a sweet little baby?" And like Mimi like screamed at them: "I'm not a baby" to like these older ladies, so she'll get really mad.

Table 2b Examples of Aligned Child PRO and Parent ObsRO Quotes for the TB-CGHD

Domain	Item	Child Self-Report	Parent-Reported Observation
Physical	<b>In the past week, how much did your shots:</b>		
	Hurt?	Emmett: Sometimes when I tense up, it hurts a lot, and I usually like hold on to my leg because I don't want it to like hurt a lot.	Amy: It hurts. Yes, I mean she screams. She cries; it hurts. We do keep it in for six seconds and those six seconds, it hurts, and I've done a lot of reading up on it and some people say that the brand we have is the least painful. Others say it's the actual medicine going in that stings.
	Sting?	Alton: Um, the hardest thing, um - - well one of the hardest parts is when I get a new pen, like we just dial it up and do it. There's usually a few drops on the needle and that - - like it stings a lot.	Nikole: It's not the needle going in, it's the serum. It's the - - I think it's the stinging sensation of the serum and when we were taught how to give her the injection, we were taught to do it quickly, and over time we've slowed down injecting the serum into her and it has been less painful.
Emotional	<b>In the past week, how often were you:</b>		
	Worried about getting your shots?	Alexis: And when I get my shots, I've been more like braver at getting them. Like the flu shot or something, I've been so much braver now. I used to cry because I didn't like them; but now since I've been doing my shots, it doesn't bug me anymore because I know I have to do it every single day and I'm already used to it, so I become more brave, confident at getting them.	Brandi: Oh, horrible. My husband and I, it was - - just dreaded every night. We go in there at 10, and we were tired, and it's in the dark, and one of us - - he had to hold him down because he knew he was going to flip out while I did the injection.
	Embarrassed because you take shots to grow?	Julian: I don't want them to know that I get jabs every night, because I am afraid they might laugh at me.	Lisa: Not that I've seen, not in front of me. He has asked me not to say something and not to talk about it to a parent, which kind of - - you know if we were going somewhere, would you please don't say it to so and so, and so that's what made me believe that he doesn't even - - his friends don't know.
Interference	<b>In the past week, how often did you:</b>		
	Try to avoid or delay getting your shots?	Franzi: That I sometimes simply don't want to do it... I just run away somewhere.	Brandi: He ices it down, and then I'll pull the ice off sometimes and say, "Okay." And he'll say "No, no, no. I'm not ready. I'm not ready."
	Miss doing things because of your shots?	Jennifer: Yes, when I'm having a sleepover it kind of annoys me when I have to always come home and get my jag and then go all the way back up to my friends.	Michelle: That's okay. Um, so a lot of times he won't stay at a friend's house because I can't just go, give him the shot and come home, or if he's spent the day there and wants to stay, I have to run that over, do it, come back home, so sometimes it's just easier just to go get him, bring him home and just be done.

Figure 1 Examples of PRO and ObsRO versions of the TRIM-CGHD

These questions are about you and what you think and feel. Please mark an "x" in one box only for each question. Don't worry, this is not a test. There are no right or wrong answers. We will not tell anyone how you answered these questions. Please think about the PAST WEEK (7 days) when answering these questions.

**In the past week, how hard was it:**

1. To keep going when doing sports or other physical activities ...

2. To concentrate ...

3. For you to fall to sleep or stay asleep all night ...

4. To focus on what you were doing ...

**In the past week, how often did you:**

5. Get out of breath when doing sports or other physical activities ...

**In the past week:**

6. How strong was your body when doing sports or other physical activities ...

7. How tired were you during the day ...

The following questions are about the impact of growth hormone deficiency (GHD) on your child's functioning and wellbeing. When answering the questions, please check the response box that most closely represents what you have SEEN or BEEN TOLD by your child or by others about your child. If you have not seen or been told anything which informs you how to answer a question, please check the "Don't Know" response box. Please do not answer any questions based on what you think, base your response only on what you have seen or been told.

If your child has other health conditions, please think only about their GHD when answering these questions. Please check only one response box for each question. There are no right or wrong answers to these questions.

**In the past week, how difficult was it for your child to:**

1. Keep going when doing sports or other physical activities ...

2. Concentrate ...

3. Fall to sleep or stay asleep all night ...

4. Focus on what they were doing ...

**In the past week, how often did your child:**

5. Get out of breath when doing sports or other physical activities ...

**In the past week:**

6. How physically strong was your child when doing sports or other physical activities ...

7. How tired was your child during the day ...

## Conclusions

- It is possible to elicit ObsRO data from parents of young children with GHD and design scientifically valid:
  - GHD PRO disease and treatment burden outcome measures appropriate for children ages 9 to <13 years, which are understandable, relevant, and easily answered by the child without help from others
  - ObsRO versions of these measures, which can be completed by parents of children with GHD ages 4 to <9 years
- Collection of both child PRO and parent ObsRO data from outcome measures developed using this methodology will allow:
  - For the inclusion of disease and treatment burden outcome data for young children in the drug development process
  - Clinicians to assess treatment benefit for their GHD patients
  - Researchers to design studies, which capture disease and treatment burden outcome data about younger children

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