Development of the Hypoparathyroidism Daily Diary of Symptom Experience (HPT-DD-SE) and the Hypoparathyroidism Life Impact Questionnaire (HPT-LIQ)

Crawford R,[1] Allas S,[2] Morrison R,[1] Tremel N,[2] Weiss B,[2] Robo C,[2] Murphy D,[3] Doward L[1]

[1] RTI Health Solutions, Manchester, United Kingdom; [2] Amolyt Pharma SAS, Lyon, France; [3] Hypoparathyroidism Association, Inc., Lemoore, California, United States

BACKGROUND

- Hypoparathyroidism (HPT) is a rare endocrine condition characterized by fluctuations in calcium levels.[1] Weekly or sometimes daily decreases in calcium levels can potentially be life-threatening.[2]
- HPT results in neuromuscular, neurological, and cardiovascular issues that can range in intensity and impede patients' ability to function in their everyday lives.[2-5] Challenges for patients with HPT include daily symptom control and the prevention of long-term complications.[2] HPT symptoms can have a profound impact on many aspects of patients' day-to-day lives.[5]

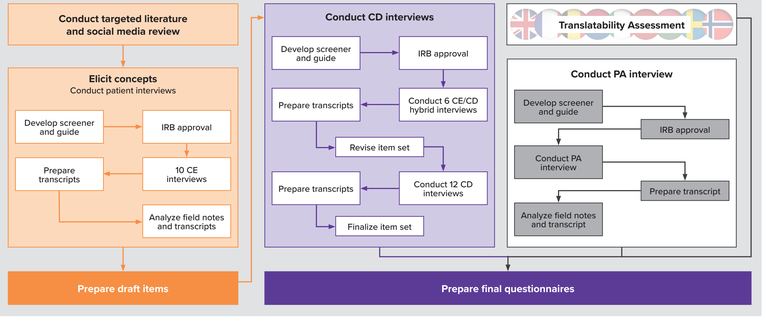
PURPOSE

- To develop HPT-specific patient-reported outcome (PRO) measures to assess the effect of investigational treatment on symptoms and health-related quality of life (HRQOL).
- This study reports on the initial development of the Hypoparathyroidism Daily Diary of Symptom Experience (HPT-DD-SE) and the Hypoparathyroidism Life Impact Questionnaire (HPT-LIQ).

METHODS

- The development of the HPT-DD-SE and HPT-LIQ followed a rigorous process (Figure 1) in accordance with the United States (US) Food and Drug Administration (FDA) PRO and Patient-Focused Drug Development guidance documents intended to support labeling claims and in line with the European Medicines Agency (EMA) reflection paper on the use of HRQOL measures in the drug evaluation process.[6-8]
- The social media review was reviewed by RTI International's (RTI's) institutional review board (IRB), which determined that it did not constitute research with human subjects (STUDY00021299). All qualitative interviews (concept elicitation [CE], cognitive debriefing [CD], and patient advocate [PA]) were also reviewed and granted approval from RTI's institutional review board (IRB) (STUDY00021403).
- Patients with HPT were recruited via a medical recruitment agency and the US HypoPARAthyroidism Association, Inc.

Figure 1. Development of the HPT-DD-SE and the HPT-LIQ



Item Generation

- Targeted literature and social media reviews were conducted to identify a preliminary list of key concepts of importance to patients with HPT.
- Semistructured CE interviews were conducted with patients who met the interview inclusion criteria (Table 1). Interviews were audio-recorded, and transcripts were produced.
- Thematic analysis was conducted on the interview transcripts to evaluate key areas of symptomatic and HRQOL impact from the patient perspective.[9]
- A conceptual model for HPT developed from the thematic analysis was used to guide item selection for the draft PRO instruments (HPT-DD-SE and HPT-LIQ).

Table 1. Study Inclusion/Exclusion Criteria

Inclusion criteria	Exclusion criteria
Adults aged ≥ 18 years with self-reported HPT for ≥ 12 months currently taking active vitamin D supplements (e.g., calcitriol or alfacalcidol) and supplemental oral calcium (based on self-report)	Patients with a self-reported history of autosomal-dominant hypocalcemia or pseudohypoparathyroidism, or those dependent on regular parenteral calcium infusions (e.g., calcium gluconate) to maintain calcium homeostasis (based on self-report) or with self-reported previous treatment with PTH-like drugs—including PTH(1-84), PTH(1-34), or abaloparatide—within 3 months prior to screening for CE interviews and within 1 month prior to screening for the hybrid CE/CD and CD interviews
Patients able to speak, read, and understand English and able to participate in web-based, English-language research interviews	

PTH = parathyroid hormone.

Content Validity

- The content validity of the draft HPT-DD-SE and HPT-LIQ was evaluated via 1 round of hybrid CE/CD interviews and 2 rounds of CD interviews with patients with HPT who met the interview inclusion criteria (Table 1).
  - The CE component of the CE/CD hybrid interviews was used to confirm and support the findings from the full CE interview stage.
  - The CD interviews tested the draft PRO instruments, informed revisions of the instructions and questions, and identified optimal response scales.
- Three rounds of interviews were conducted to allow for changes to be made to the instruments and tested in the subsequent rounds of interviews.
- A single interview with a US-based PA with a self-reported diagnosis of HPT was also conducted to provide insights into the experiences of the wider HPT community to confirm and support the findings from the patient interviews.

Translatability Assessment

- Consistent with best practices for PRO instrument development,[10] a translatability assessment (TA) was conducted for the US-English versions of the HPT-DD-SE and HPT-LIQ to facilitate future translation and use of the HPT-DD-SE and HPT-LIQ external to the US.
- The TA focused on identifying any potential challenges for translation of item wording (language or concepts) and response options/scales for 9 European countries: the United Kingdom (English), France (French), Belgium (French/Flemish), the Netherlands (Dutch), Italy (Italian), Spain (Spanish), Hungary (Hungarian), Sweden (Swedish), and Norway (Norwegian).

RESULTS

Patient Sample

- The CE sample included 10 patients, the CE/CD hybrid sample included 6 patients, and the CD sample included 12 patients (Table 2).

Table 2. Patient Interview Sample Characteristics

Sample characteristic	CE sample (N = 10)	Hybrid CE/CD (CD round1) (N = 6)	CD round 2 sample (N = 6)	CD round 3 sample (N = 6)
Female, n (%)	9 (90.0)	6 (100.0)	6 (100.0)	5 (83.3)
Age, mean (SD) [range]	51.8 (16.0) [27-76]	47.0 (15.0) [26-64]	46.3 (11.5) [32-64]	52.3 (14.9) [41-72]
Race, n (%)				
Black or African American	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
White	8 (80.0)	5 (83.3)	6 (100.0)	6 (100.0)
Other	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic or Latino	1 (10.0)	1 (16.7)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	9 (90.0)	5 (83.3)	6 (100.0)	6 (100.0)
HPT caused by surgery, n (%)	5 (50.0)	4 (66.7)	5 (83.3)	5 (83.3)
Length of HPT diagnosis, mean (SD)	13.1 (12.7)	7.5 (8.8)	12.3 (17.3)	14.9 (10.6)
Other health conditions, n (%)				
Back pain	3 (30.0)	1 (16.7)	2 (33.3)	1 (16.7)
Depression	5 (50.0)	1 (16.7)	4 (66.7)	1 (16.7)
High cholesterol	4 (40.0)	1 (16.7)	1 (16.7)	3 (50.0)
Hypothyroidism	9 (90.0)	4 (66.7)	3 (50.0)	5 (83.3)
Osteoarthritis	3 (30.0)	2 (33.3)	2 (33.3)	0 (0.0)
Reflux disease	7 (70.0)	2 (33.3)	0 (0.0)	1 (16.7)
Thyroid disease	8 (80.0)	4 (66.7)	5 (83.3)	2 (33.3)
Type 2 diabetes	2 (20.0)	0 (0.0)	1 (16.7)	0 (0.0)
Other	9 (90.0)	5 (83.3)	5 (83.3)	3 (50.0)

SD = standard deviation.

Item Generation

Targeted Literature Review (Development of Preliminary Item Content)

- The literature review identified 12 publications reporting key concepts of importance to patients with HPT.
- The social media review identified 43 posts (11 videos and 32 blogs) containing online stories from 52 individual contributors (43 female, 7 male, and 2 not reported).
- Key symptoms and impacts important to patients with HPT were identified based on the results of the reviews of the published literature and social media data (Figure 2).
- A preliminary list of questionnaire items was developed based on the findings from the targeted literature, social media, and PRO instrument reviews.

Figure 2. Key Symptoms and Health-Related Quality of Life Impacts

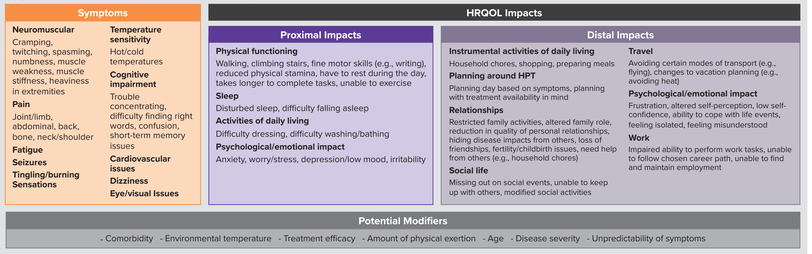
Development of Draft HPT PRO Measure

- The CE interviews revealed that HPT has a detrimental impact on many aspects of patients' lives, including physical impacts on mobility and ability to function and impacts on relationships and social functioning.
- The symptomatic and HRQOL impacts of HPT have been described in detail in a previous publication[11] and are summarized in Table 3.

Table 3. Patient Interview Sample Characteristics

Key Symptoms Reported by ≥ 7 Patients	Key Patient-Reported HRQOL Impacts of HPT
Cognitive dysfunction (n = 10; 100%), pain (n = 10; 100%), muscle cramps (n = 10; 100%), fatigue (n = 10; 100%), muscle twitches/spasms (n = 9; 90%), temperature sensitivity (n = 9; 90%), tingling (n = 8; 80%), muscle weakness (n = 8; 80%), and muscle stiffness (n = 7; 70%)	Physical functioning (n = 9; 90%), daily activities (n = 10; 100%), social functioning/ relationships (n = 10; 100%), emotional impact (n = 10; 100%), work (n = 8; 80%), and sleep (n = 5; 50%).

Figure 3. Hypothesized Conceptual Framework, HPT (Detailed)



Instruments: Draft, V1.0

- The preliminary item list was revised to include the concepts that emerged from the CE interview data as important to patients and was refined using the words and phrases expressed by patients during the CE interviews.
- 2 HPT-specific PRO measures were developed (Table 4).

Table 4. Draft HPT-DD-SE and HPT-LIQ (V1.0)

HPT-DD-SE (V1.0)	HPT-LIQ (V1.0)
• 19 items • Symptom severity • 24-hour recall period • 11-point numeric rating scale • Daily diary: anticipated to be completed every day for 7 days before each the assessment day	• 34 items • Severity of impact on HPT-related HRQOL (physical functioning, daily activities, social functioning, psychological/emotional impact, work and employment, and sleep) • 7-day recall period • 4- or 5-point verbal rating scale • Anticipated to be complete once during the assessment day

- Table 5 illustrates the anticipated daily administration schedule for the HPT-DD-SE and the HPT-LIQ. On Day 1 through Day 7, the patient completes the HPT-DD-SE questions based on the last 24 hours. It is recommended that patients complete the HPT-DD-SE at the same time every day.
- The draft measures included some duplicate items to allow patient-selection of most appropriate phrasing during CD interviews.

Table 5. HPT-DD-SE and HPT-LIQ Anticipated Administration Schedule

Measure	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7[a]
HPT-DD-SE	X	X	X	X	X	X	X
HPT-LIQ							X

[a] Day 7 will coincide with patients' scheduled clinic visit or assessment day.

Content Validation

- Similar symptoms and HRQOL impacts emerged from the 6 hybrid CE/CD interviews and were confirmed by the PA.
- The draft measures were also reviewed by a US-based HPT PA to assess face validity. The selected recall periods and respective response formats were supported by the US PA advising on the instrument development process.
- Figure 5 presents the iterative approach of the CD interviews and the revisions made to each iteration of the draft COA instruments following each round of CD interviews as well as the TA and expert review.
- Participants across all 3 rounds of interviews found the content of the HPT-DD-SE and the HPT-LIQ to be relevant, clear, understandable, and comprehensive.
- The CD interviews confirmed content validity, resulting in a 15-item HPT-DD-SE (V4.0) and a 27-item HPT-LIQ (V4.0).
- Changes were based on patient preferences for item relevance and comprehension. The final versions were acceptable to patients.

Figure 5. HPT-DD-SE and HPT-LIQ Development Process

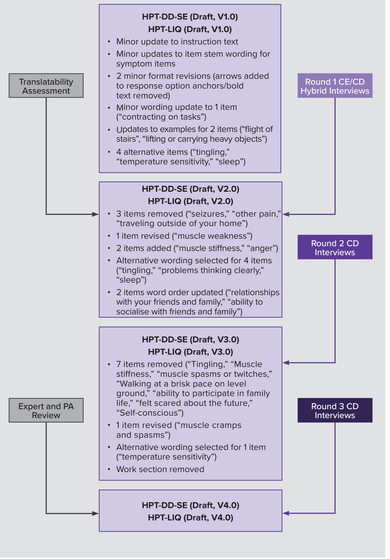
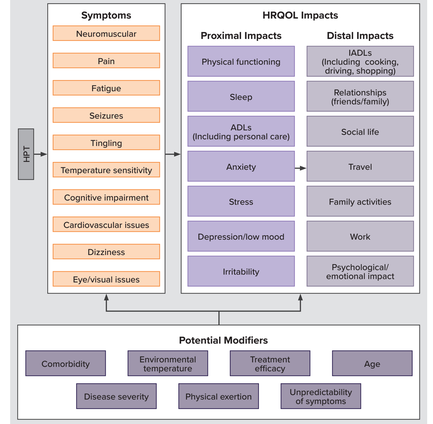


Figure 4. Draft Summary Conceptual Model, HPT (Summary)



ADL = activity of daily living; IADL = instrumental activity of daily living.

CONCLUSIONS

- The CE interviews identified keys symptoms and broader HRQOL impacts of HPT that are important to patients.
- The rigorous development process yielded 2 HPT-specific PRO measures: the HPT-DD-SE assesses severity of key symptoms (last 24 hours), and the HPT-LIQ assesses HRQOL impacts of HPT (last 7 days).
- The inclusion of a TA early in the development of the new HPT-specific PRO instruments will help maximize the cross-cultural applicability of the instruments.
- Further work is needed to assess the psychometric properties of the new measures.

REFERENCES

1. National Organization for Rare Diseases. Hypoparathyroidism. https://rarediseases.org/rare-diseases/hypoparathyroidism/. **2.** Murphy D, et al. J Endocrine Soc. 2021;5(Suppl 1):A260-1. **3.** Astor MC, et al. J Clin Endocrinol Metab. 2016;101(8):3045-53. **4.** Shoback DM, et al. J Clin Endocrinol Metab. 2016;101(6):2300-12. **5.** Brod M, et al. Patient. 2020a;13(2):151-62. **6.** FDA. https://www.fda.gov/media/77832/download. **7.** FDA. https://www.fda.gov/media/139088/download. **8.** EMA. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-guidance-use-healthrelated-quality-life-hrql-measures-evaluation_en.pdf. **9.** Braun V, et al. Qual Res Psychol. 2006;3(2):77-101. **10.** Patrick DL, et al. Value Health. 2011;14(8):978-88. **11.** Crawford R, et al. Living with an "invisible disease": a qualitative study with patients with hypoparathyroidism. Poster presented at ENDO 2022; 11 June 2022.

ACKNOWLEDGMENTS

The authors express their gratitude to the patients who contributed to the research.

FUNDING

This study was funded by Amolyt Pharma SAS, Lyon, France.

CONTACT INFORMATION

Rebecca Crawford, MA
Director
RTI Health Solutions
2nd Floor, The Pavilion, Towers Business Park, Wilmslow Road, Didsbury, United Kingdom
Email: rcrawford@rti.org

Presented at the American Society for Bone and Mineral Research 2022 Annual Meeting; 9-12 September 2022; Austin, Texas, United States