The International Development of the Modified Hyperphagia Questionnaire

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BACKGROUND

Beloranib, a methionine aminopeptidase 2 inhibitor, is in development for the treatment of hyperphagia-related behaviors and obesity in individuals with Prader-Willi syndrome (PWS). PWS is a complex, rare genetic disorder that has multiple systemic effects. The hallmark of PWS is an incessant feeling of insatiable hunger, regardless of food intake (hyperphagia). Patients typically also have abnormal growth and development, intellectual disabilities, maladaptive and compulsive behaviors, and severe obesity without institution of behavioral adaptations that significantly impact the quality of life of the entire family. Due to their cognitive limitations, individuals with PWS are unable to reliably report the severity of their hyperphagia. Thus, a caregiver-reported measure focused on food-seeking behaviors is needed to support pharmaceutical development and labeling claims associated with hyperphagia in this patient population. The caregiver-completed Hyperphagia Questionnaire (HQ) is a 13-item instrument currently available in United States (US)-English, commonly used to assess food-seeking behaviors in PWS research.[1]

OBJECTIVE

To develop and culturally adapt a modified version of the HQ, the HQ for Clinical Trials (HQ-CT), for use in multinational PWS clinical trials.

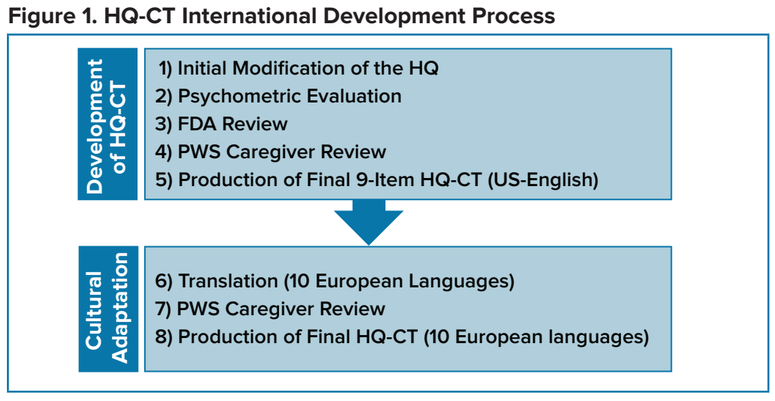
METHODS

The international development of the HQ-CT comprised two key stages: the development of the HQ-CT in US-English and the cultural adaptation of the US-English HQ-CT into 10 European languages (Figure 1).

Development of the HQ-CT in US-English

1) Initial Modification of the HQ

Figure 1. HQ-CT International Development Process



- The developers of the HQ and experts in clinical outcome assessments reviewed the HQ considering industry guidance related to clinical outcome assessments, including recommendations in the Food and Drug Administration (FDA) patient-reported outcome guidance.[2] The objectives were to limit the concepts of measurement to behaviors that are observable by caregivers and that have the potential to change during the course of the trial.

2) Psychometric Evaluation

- The preliminary HQ-CT underwent psychometric evaluation using data collected in a phase 2, single-center, randomized, double-blind, placebo-controlled clinical trial of beloranib in patients with PWS. Analyses evaluated the internal consistency of composite HQ-CT scores (Cronbach's alpha), construct validity (Spearman correlations with additional measures), and preliminary responsiveness (effect size estimates for HQ-CT items). Item-total correlations and inter-item correlations were computed to inform the HQ-CT scoring algorithm. Due to small sample sizes, Cohen's general rule of thumb was applied to characterize effect size estimates in change scores (i.e., 0.20, small; 0.50, moderate; 0.80, large).

3) FDA Review

- A review of the modified HQ-CT was conducted by the FDA.

4) PWS Caregiver Review

- The aim of the interviews was three fold: to inform any further refinements to facilitate ease of item comprehension and response by caregivers, to provide additional support for content validity of the HQ-CT, and to optimize the usability of the electronic-data-capture device.
- In-depth qualitative interviews were conducted with 6 caregivers of overweight or obese adolescents or adults with PWS. The interviews had two main components: a concept elicitation interview and cognitive debriefing of an electronic version of the HQ-CT.

5) Production of Final 9-Item HQ-CT (US-English)

- The results from the initial modification of the original HQ were combined with the findings from the psychometric evaluation, FDA review, and caregiver review to transform the HQ into the HQ-CT.

Cultural Adaptation of HQ-CT into 10 European Languages

- Industry-standard adaptation methods were used to ensure conceptual equivalence between the new language versions and the original source US-English instrument, while using everyday language suitable for the target culture.3 The cultural adaptation process included two key stages: initial translation and PWS caregiver review.

6) Translation

- Translation of the HQ-CT into the 10 European target languages used a forward-back translation methodology, which was aided by a comprehensive instrument codebook. The process for producing the initial translations for all language versions involved the following steps: forward translation, harmonization, backward translation, conceptual equivalence review, and final adjustments (if needed).

7) PWS Caregiver Review

- Individual cognitive debriefing interviews were conducted with 5 caregivers of patients with PWS in each target country to assess the face and content validity of the translated HQ-CT.

RESULTS

Development of the HQ-CT in US-English

1) Initial Modification of the HQ

- A preliminary 10-item HQ-CT was created following the development and expert review of the original 13-item HQ.
- Initial modifications transformed the HQ into the preliminary 10-item HQ-CT. Three items were eliminated based on content. Concepts were limited to behaviors observable by caregivers. Recall period was reduced to 2 weeks and the response scales revised accordingly.

2) Psychometric Evaluation

- The psychometric evaluation of the 10-item HQ-CT supported the use of a single composite score in future trials and provided evidence of the measure's reliability and construct validity.
- All average item scores improved (decreased) over time, and the magnitude of change was small. All inter-item correlations were positive, and a majority of correlations were moderate to strong in magnitude. The unidimensionality of the scoring structure was supported by alpha estimates ranging from 0.87 to 0.92 across assessment time points. The HQ-CT total score was able to differentiate between the placebo and pooled treatment groups based on improvements in hyperphagia-related behavior.

3) FDA Review

- The FDA identified one item for elimination, stating that the underlying concept was similar to that addressed by another item. The emphasis in the item identified for deletion was considered to be focused on the interaction between the caregiver and the patient, rather than on the patient's behavior. Consequently, this item was removed with agreement from the HQ developers, resulting in a 9-item version of the HQ-CT.

4) PWS Caregiver Review

- Four of the 6 caregivers who participated in the qualitative interviews were female. The individuals with PWS under the care of the participating caregivers had a mean age of 32.7 (range: 22.0-44.0).
- Overall, caregivers found the 9-item HQ-CT to be clear and easy to understand. Content was considered relevant, and the 2-week recall period was reported to be appropriate and easy to reference. All caregivers reported that the most important concepts in terms of food-related behaviors were captured by the HQ-CT. Only minor wording changes were made to the HQ-CT as a result of the caregiver review.

5) Production of Final 9-Item HQ-CT (US-English)

- The results from the initial modification of the original HQ were combined with the findings from the psychometric evaluation, the FDA review, and the caregiver review to culminate in the production of the final 9-item HQ-CT.

Cultural Adaptation of HQ-CT into 10 European Languages

6) Translation

- The HQ-CT, including instructions, items, and response options, was translated into 10 European target languages with little difficulty. All translation issues were resolved, and a review of the back translations confirmed conceptual equivalence of the source version of the HQ-CT and the new preliminary translations.

7) PWS Caregiver Review

- Table 1 shows the characteristics of the caregivers interviewed.

Table 1. Demographics Characteristics Cognitive Debriefing Interviews

Country-Language	Sex	Age in Years Mean (Range)
Belgium-Dutch	1M:4F	35.2 (34-47)
Belgium-French	2M:3F	39.4 (24-59)
Denmark-Danish	3M :2F	49.0 (33-64)
France-French	2M:3F	37.8 (25-52)
Germany-German	1M:4F	50.4 (45-57)
Italy-Italian	2M:3F	45.0 (41-53)
Netherlands-Dutch	0M:5F	28.8 (23-52)
Spain-Spanish	3M:2F	43.0 (40-46)
Sweden-Swedish	2M:3F	46.0 (33-61)
UK-English	0M:5F	44.0 (36-58)

M = male; F = female.

- Caregivers in each target country found the HQ-CT easy to understand and culturally appropriate. Two modifications were made to all 10 new language versions:
  - The acronym HQ-CT was removed from the questionnaire title, as this was considered distracting by several caregivers.
  - Several caregivers reported a lack of familiarity with the term "hyperphagia" in the opening instructions. Supplementary text was added, as shown in the bold underlined text in Box 1.

Box 1. Revised HQ-CT Instructions

Evaluating food-related problem behaviors is an important part of this study. Please take your time to think carefully and in some detail about the last 2 weeks of hyperphagic **(intense, incessant sensation of hunger)** and food-related behaviors shown by the person with PWS in your care. Be sure to consider the full 2-week period including nights and weekends, seeking input from other caregivers as necessary. Please be as accurate and as honest as you can, without minimizing or over-inflating the person's behaviors.

- Additional, minor modifications were made to individual language versions to improve clarity or grammatical accuracy (Table 2).

Table 2. Country-Language Specific Modifications

Country-Language	Revision
Denmark-Danish	The HQ-CT response option "Lidt" (A little) was changed to "En smule" (A bit) to increase conceptual clarity.
France-French	The word "exprimé" (become) was replaced with "exprimée" to improve grammatical accuracy in HQ-CT item 1 and item 8.
Italy-Italian	A comma was added after "apparenza" (appear) in HQ-CT item 8 to improve conceptual clarity.
Netherlands-Dutch	The term "de" (the) replaced "deze" (this) as the more appropriate term in HQ-CT item 1.

CONCLUSIONS

The qualitative and quantitative evidence presented supports the use of the 9-item HQ-CT to assess hyperphagia in international PWS clinical trials. The comprehensive cultural adaptation methodology helped to ensure that the new language versions were conceptually equivalent to the source instrument and appropriate to each target culture. The development of the HQ-CT and its cultural adaptation to 10 European languages, with input from 56 caregivers, produced a valuable instrument for assessing food-seeking behaviors in PWS clinical trials in the US and Europe.

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