

Harnessing the power of patients: Developing and validating the Neuronopathic Gaucher Disease Patient Reported Outcomes (nGD-PRO) and Observer Reported Outcomes (nGD-ObsRO) to measure HRQoL in patients with Gaucher Disease Type 2 and Type 3

Kathleen Beusterien¹, Jason Isaacs¹, Dena Jaffe¹, Deborah Elstein², Maddie Stoodley³, Elin Haf Davies ⁴ Tanya Collin-Histed³

1 Cerner Enviza, 2 Shaare Zedek Medical Center, 3 International Gaucher Alliance, 4 Aparito

Background

- Three clinical forms of Gaucher Disease (GD), a rare inherited metabolic disorder, are defined based on the absence (type 1, GD1) or presence (types 2 and 3, neuronopathic GD, nGD) of neurological signs.
- General health-related quality-of-life (HRQoL) measures may lack sensitivity in capturing outcomes specific to nGD.

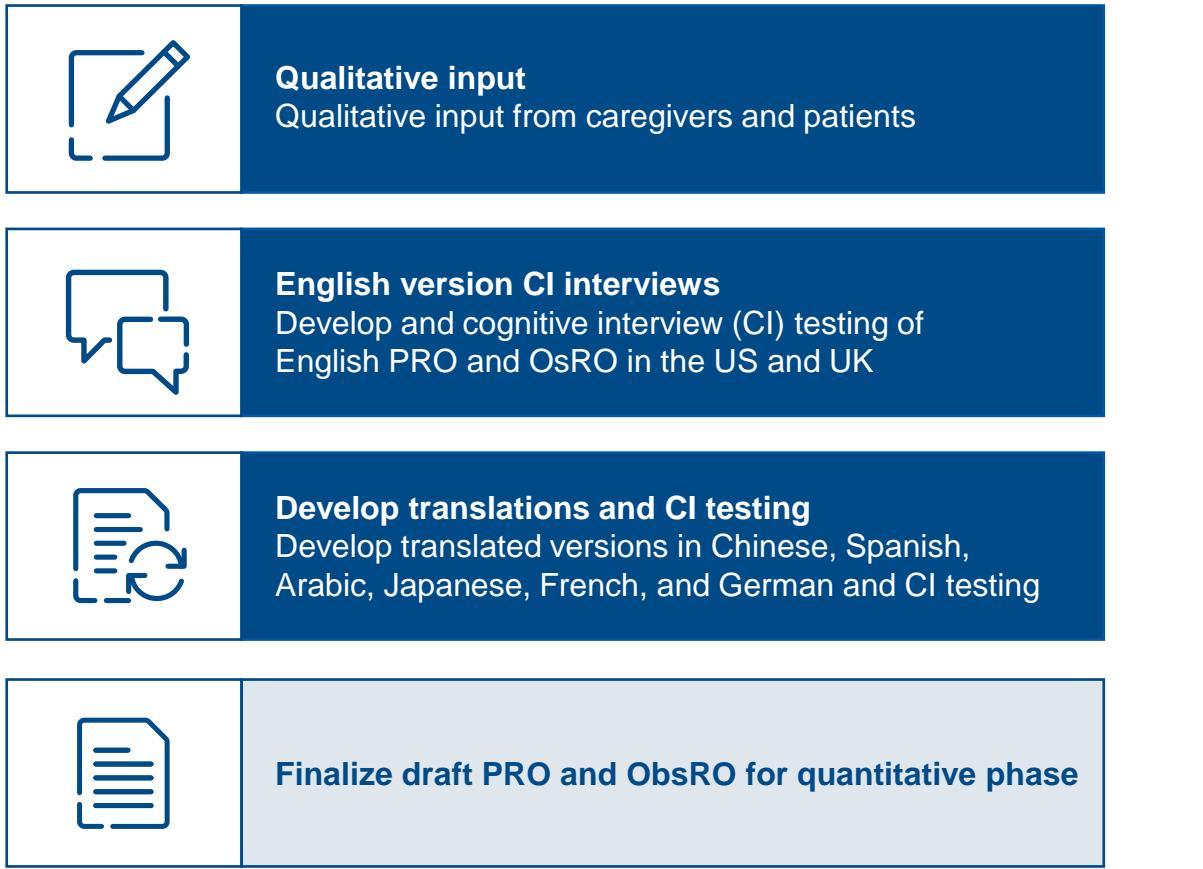
Objective

- To develop and assess the content validity of a nGD-specific patient-reported outcomes (PRO) and observer-reported outcomes (ObsRO) measure in partnership with patients, caregivers, and other stakeholders.

Methodology

- This research involved three phases spanning over 3.5 years: 1) Qualitative input to inform content of draft nGD PRO and ObsRO; 2) Cognitive interview testing of English versions; and 3) Development of translations and cognitive interviews (Figure 1).
- The International Gaucher Alliance (IGA) led all recruitment efforts. They identified and recruited a global group of clinical experts. With respect to patients and caregivers, on-line social media platforms (Facebook and Twitter) were used to distribute the opportunity to volunteer to take part. Most qualitative interviews with patients/caregivers were held online using Zoom.
- The cognitive interviews to test the draft measures were conducted by trained moderators in each respective country; they conducted telephone interviews to obtain feedback on the draft PRO and ObsRO measures, which were shared on a screen-sharing platform.
- The cognitive interview protocol received exemption status from Pearl IRB, 05 March 2021.

Figure 1. PRO and ObsRO development and content validation steps



Phase 1: Qualitative input

- The International Gaucher Alliance (IGA) led a comprehensive literature review, consensus rounds with clinical experts in-person or remotely, and interviews with caregivers and patients to identify concepts for inclusion in the PRO and ObsRO (Table 1).
- 21 clinical experts participated from Egypt, Germany, Japan, UK, US, France, Pakistan, and Spain.
- Seven parents (two fathers, five mothers) and three patients (all female) participated from the UK, Japan, and Sweden. The age range of the individuals living with nGD ranged from 2 to 25 years of age.
- To help confirm key outcomes from the qualitative research, a global online survey was implemented, of which 10 patients and 20 carers took part.

Table 1. Neuronopathic symptoms and impacts identified by patients and caregivers

| Concept | Expert Input | Patient/ Caregiver Input |
|--|--------------|--------------------------|
| Symptoms | | |
| Fatigue | X | X |
| Pain in small joints | X | |
| Pain in large joints | X | |
| Speech/initiate conversation | | X |
| Salivation/drooling | X | X |
| Chewing/swallowing/choking | X | X |
| Bone/muscle pain, including back pain | X | X |
| Nerve pain | X | X |
| Seizure/jerky movements | X | X |
| Trouble concentrating/staying focused | | X |
| Feeling overwhelmed/memory trouble | | X |
| Physical Function | | |
| Sitting | X | X |
| Using utensils/writing | X | X |
| Balance/coordination/feel wobbly | X | X |
| Walking | X | X |
| Reaching for objects independently | X | |
| Self-Care | | |
| Dressing | X | X |
| Hygiene | X | X |
| Toileting | X | |
| Prepare food | | X |
| Daily and Social Activities | | |
| Attending school/work | X | X |
| Recognizing significant others | X | X |
| Performing hobbies | | X |
| Feelings about relationships/friendships | | X |
| Sleeping | | X |
| Emotional Impacts | | |
| Irritability/anger | X | X |
| Anxiety | X | X |
| Feel very low/down | X | X |
| Happy/positive | X | X |
| School/work stress | | X |
| Stressful traveling outside of home | | X |
| Concern about treatment side effects | | X |
| Concern about caregiver burden | X | |
| Support Services/Coping | | |
| Accommodations made at school/work | | X |
| Receiving/using emotional support | | X |
| Receiving physical support services | X | X |
| Connected to others with Gaucher Disease | | X |
| Supportive healthcare providers | | X |
| Clinical study participation | | X |
| Caregiver Impacts | | |
| Stress in caregiving | X | X |
| Stress in traveling with patient | | X |
| Fatigue | X | X |
| Anxious about patient's health | X | X |
| Positive/hopeful about patient's health | X | X |

Fatigue

"Her first wheelchair when she was about 7 was because of fatigue."

Bone/muscle pain, including back pain

"I suffer with really extreme severe bone pain. It sort of varies throughout the body, but I would say the main bit I have is in my lower spine."

Balance/coordination/feel wobbly

"Sometimes I lose my balance; my feet sort of flick to the side or flick inwards, which makes me stumble."

Hygiene

"I struggle with sort of say like zips, buttons, that kind of thing."

Feelings about relationships/friendships

"It's quite hard to make friends. The mainstream friends that you have, they are off on their fast pace of life."

Anxiety

"I was constantly feeling sort of on edge, panicky. I wouldn't leave the house without feeling like something bad was going to happen."

Phase 2: English version CI interviews

- The patient and caregiver feedback and qualitative input informed the development of draft PRO and ObsRO measures
- Table 2 lists the scales and respective number of items in each measure
- The recall period for each item is the past 14 days. All item response scales, with the exception of Support services, are 10-point scales that include interim descriptive categories to enhance interpretation of the numbers

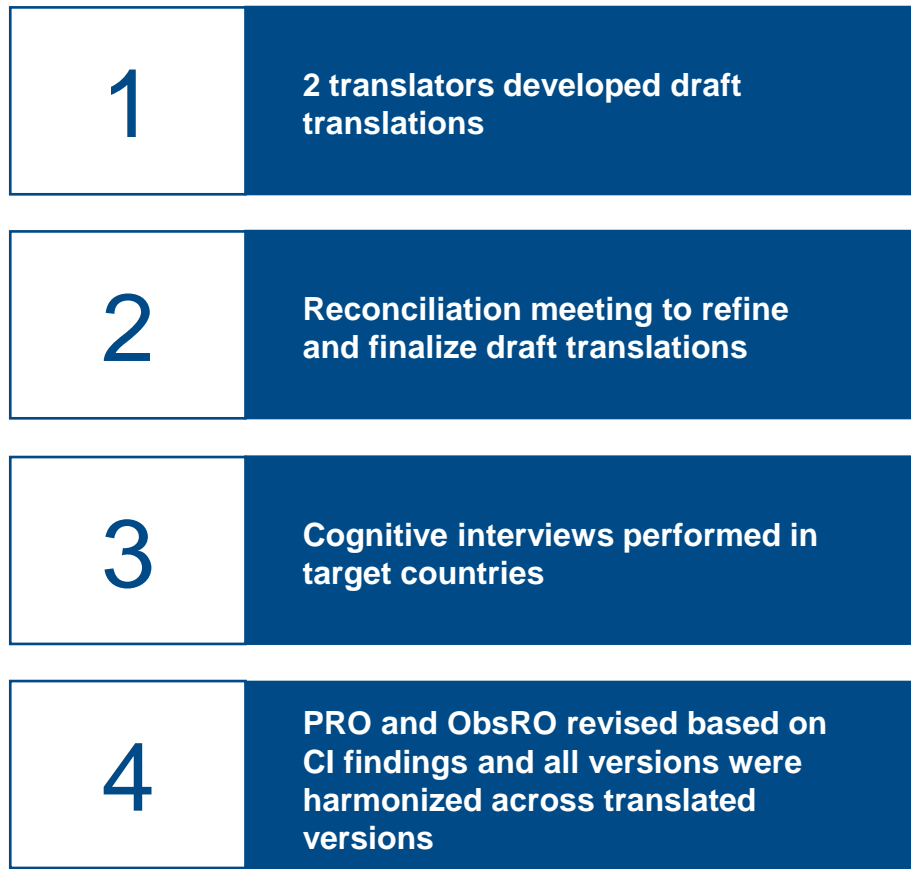
Table 2. PRO and ObsRO Scales

| Scale | Items per scale |
|----------------------------------|-----------------|
| PRO and ObsRO | |
| Symptoms | 8 |
| Physical functioning | 5 |
| Self-care | 4 |
| Feelings | 4 |
| Daily and social activities | 5 |
| Concerns about medications | 2 |
| Support services | 5 |
| Overall health | 1 |
| ObsRO Only | |
| Time spent with patient with nGD | 2 |
| Caregiver impacts | 4 |

Phase 3: Develop translations and CI testing

Based on the feedback from the CI interviews with caregivers and patients in the US and UK, translations were developed of the PRO and ObsRO for each target language: French, German, Spanish, Arabic, Japanese, and Chinese (Figure 2)

Figure 2. Translation steps for PRO and ObsRO



- Nine caregivers and six patients from the US, UK, China, Mexico, Egypt, and Japan participated in the CI interviews (Table 3).
- Although no participants were recruited from France or Germany, the French and German translated versions were revised accordingly based on the feedback from the other participating countries.

Table 3. Cognitive Interview Participants

| Subject Number | Patient age | Patient gender | Caregiver (age) |
|--------------------------------------|-----------------|----------------|-----------------|
| UK (3 CGs, 2 PTs) | | | |
| CG_UK_01 | 11 | Female | Mother (36 yrs) |
| CG_UK_02 | 24 | Male | Father (63 yrs) |
| CG_UK_03 | 4 | Male | Mother (36 yrs) |
| PT_UK_01 | 24 | n/r | n/a |
| PT_UK_02 | 26 | n/r | n/a |
| US (1 CG) | | | |
| CG_US_01 | 13 | Male | Mother (50 yrs) |
| Chinese (2 CGs, 1 PT) | | | |
| PT_CH_01 | 25 | Male | Father (53 yrs) |
| CG_CH_01 | 13 | n/r | Father (38 yrs) |
| CG_CH_02 | 11 | Male | Mother (42 yrs) |
| Spanish (Mexico) (1 CG, 1 PT) | | | |
| PT_MX_02 | 16 ^a | Female | n/a |
| CG_MX_01 | 16 ^a | Female | Father (59 yrs) |
| Arabic (Egypt) (1 CG, 1PT) | | | |
| CG_EG_01 | 14 ^b | Male | n/a |
| PT_EG_01 | 14 ^b | Male | Mother (42 yrs) |
| Japan (1 CG) | | | |
| CG_JP_01 | 7 | Male | Father (40 yrs) |

^a Same patient
^b Same patient

n/r= Not reported
n/a= Not applicable

- Overall, the PRO and ObsRO were well-received. Minor refinements in wording to some items were made based on the feedback (Table 4).

" The caregivers are very grateful that we can pay attention to this disease, and they think that the questionnaire is very comprehensive and asks about the things that patients usually experience."

(Moderator in China)

Table 4. Selected item revisions made based on cognitive interviews

| Original item | Issue | Revision |
|---|---|---|
| How much drooling/salivating or secretions have you experienced over the last 14 days? | PTs and CGs indicated that 'dribbling' was more aligned with disease impact versus 'salivating' | Did you have drooling or dribbling over the last 14 days? |
| Did you feel overwhelmed by too much information and/or had trouble remembering what comes next over the last 14 days? | Recommended asking only about trouble with memory as feeling overwhelmed can be interpreted as separate and being related to feeling stressed | Did you have trouble remembering things over the last 14 days? |
| Have you needed assistance sitting upright as in a chair over the last 14 days? | Suggested removing 'upright' as some patients cannot physically sit upright because their back is deformed due to the disease | Have you needed assistance sitting in a chair over the last 14 days? |
| How often did you prepare food or cook food without help over the last 14 days? | Suggested additional detail about needing help as well as type of meal | Overall, did you need help preparing simple meals (for example, making a sandwich) over the last 14 days? |
| Did you have difficulty performing any hobbies or your daily activities, including using a computer/iPad over the last 14 days? | Suggested clarification as this about multiple concepts, i.e., sports and daily activities; in addition, using a computer not considered hobby. | Did you have difficulty performing your choice of hobbies or activities over the last 14 days? |
| Did you feel happy or positive over the last 14 days? | The word 'positive' was not well understood among participants across countries. | Did you feel happy over the last 14 days? |

Conclusions and Next Steps

- The cognitive interviews informed key revisions, primarily simplification of wording, to ensure that all items are understandable and interpreted as intended.
- This collaboration among a full set of stakeholders resulted in nGD-PRO and nGD-ObsRO instruments that are content valid and expected to be robust measurements of disease impact.
- The nGD-PRO and nGD-ObsRO are available in English, French, German, Spanish, Arabic, Japanese, and Chinese.
- The psychometric validation of these measures will be nested within the Gaucher Registry for Development Innovation and Analysis of Neuronopathic Disease (GARDIAN), a global, prospective patient registry. Patients with nGD (aged ≥12 years), and caregivers will complete the nGD-PRO and nGD-ObsRO, respectively, at baseline, two weeks later, and every 6 months.

Acknowledgments

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