Improving the methods of vignette development for utility estimation: a case study in Pompe disease

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INTRODUCTION

- Late-onset Pompe disease (LOPD) is a rare, progressive neuromuscular disorder characterised by muscle weakness.[1] The predicted prevalence of Pompe disease (including LOPD and the less common infantile-onset form of the disease) is approximately 1 in 20–30,000; but varies by ethnicity, geography and diagnostic approach.[2–4]
- Patients with LOPD usually experience muscle weakness and breathing difficulties, impacting their health-related quality of life (HRQL) due to restrictions on activities and the impact on their emotional well-being.[5] Patients usually require mobility and respiratory support.[1]
- Obtaining utility data for economic evaluation in such a rare disease is challenging, and vignette methods are often used.
- Clinical study inclusion criteria often mean certain patients are ineligible to participate in trials.
- Vignettes are often derived from information available in published literature or a small sample of qualitative interviews, which provides limited evidence on the content validity of the health state descriptions.
- This study used patient-reported outcome (PRO) data to develop the vignette content.
- The draft vignettes were evaluated in interviews with patients and healthcare professionals (HCPs) and applied in valuation studies conducted to estimate utility values for LOPD health states.

METHODS

- Health state vignettes for adult patients with LOPD were developed to describe different stages of LOPD, defined by the patient's dependence on respiratory and/or mobility support (Table 1).

Table 1. Health states defined by assistive technology dependence

Health state	Mobility support	Respiratory support
1: No support	None	None
2: Intermittent mobility support	Use of mobility support (walking aid, wheelchair or motorised scooter) some of the time	None
3: Intermittent respiratory support	None	Use of respiratory support during the night or sometimes during the day
4: Intermittent respiratory and mobility support	Use of mobility support (walking aid, wheelchair or motorised scooter) some of the time	Use of respiratory support during the night or sometimes during the day
5: Mobility support dependent	Use of wheelchair or motorised scooter all of the time	None
6: Mobility support dependent and intermittent respiratory support	Use of wheelchair or motorised scooter all of the time	Use of respiratory support during the night or sometimes during the day
7: Mobility support dependent and invasive respiratory support dependent	Use of wheelchair or motorised scooter all of the time	Use of invasive respiratory support

Vignette development

- **Figure 1** shows an overview of the vignette development process.

Figure 1. Vignette development methodology overview
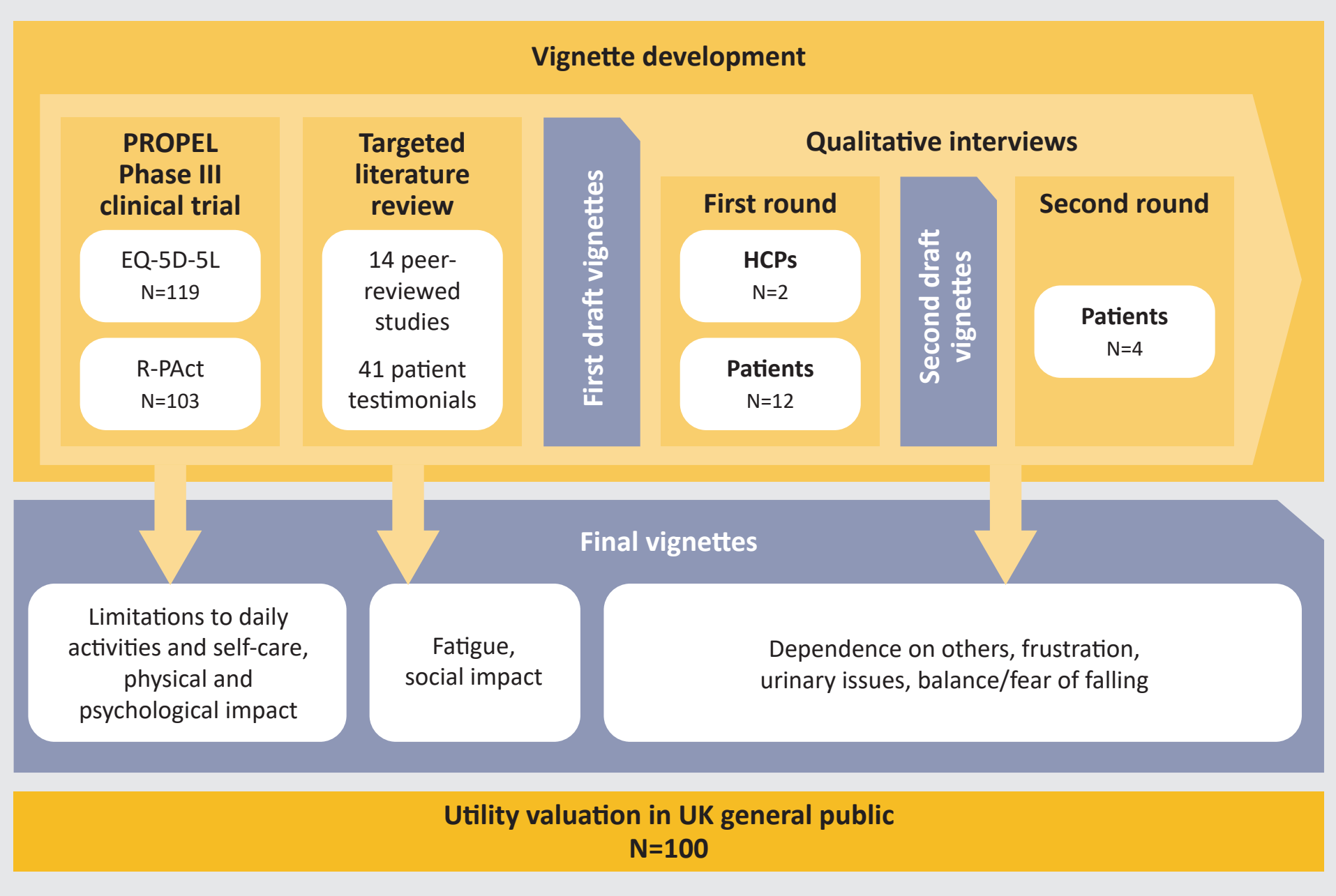
- Phase III trial (PROPEL, NCT03729362)[6] participants were classified into health states based on their documented use of mobility and respiratory support.
- Item-level response data from the Rasch-built Pompe-specific activity measure (R-PAct) and EQ-5D-5L were summarised (item level: count, percentage; item: mode, median) stratified by participants' health state classification.
- The first draft vignettes were developed using the most reported PRO item responses; missing health states and additional vignette items were supported by a targeted literature review.

Qualitative interviews

- Participants were recruited via Pompe Support UK and the Association for Glycogen Storage Disease UK (AGSD) with experience of different health states, where possible.
- Qualitative, 1-hour semi-structured interviews were conducted with patients who had a self-reported diagnosis of LOPD, were 18 or older, fluent in English, and consented to participate.
- First, participants described their experience of living with LOPD, and then provided feedback on the draft vignettes for their own current and previously experienced health states.

- All vignettes were reviewed by patients with experience of the health state except for HS7 (mobility support dependent and invasive respiratory support dependent).
- The first draft vignettes were reviewed by HCPs experienced in the treatment and management of LOPD in 1-hour semi-structured interviews.
- The vignettes were revised and finalised following HCP feedback and two rounds of patient review.

Health state utility valuation

- The health state vignettes (**Figure 2**) were valued by members of the UK general public using standard utility assessment techniques (EQ-5D-5L, Visual Analogue Scale [VAS] and Time Trade-Off [TTO] assessment).
- TTO weights were rescaled to ensure the value for the dead state was fixed at zero.
- The R package "eq5d"[7] was used to calculate EQ-5D-5L utility values using UK population weights.

Figure 2. Example health state vignette (Health state 5: mobility support dependent)

RESULTS

Health state development

- Trial data were available to inform HS1, HS2, HS3 and HS4 (**Table 2**).
- 12 patients with LOPD were interviewed. Of these, 11 described their experience of symptoms and impacts of LOPD and 9 reviewed the draft health state vignettes.
- Feedback was also obtained from 2 HCPs with ~20 years of experience managing LOPD.

Table 2. Item-level response (median) of PROPEL trial subjects on the EQ-5D-5L and R-PAct

| Characteristic	HS1	HS2	HS3	HS4
	No support	Intermittent mobility support	Intermittent respiratory support	Intermittent respiratory and mobility support
EQ-5D-5L	N=66	N=16	N=4	N=1
Mobility	2.0	3.0	4.0	3.0
Self-care	1.0	2.0	3.0	2.0
Usual activities	2.0	3.0	3.0	3.0
Pain/discomfort	2.0	2.5	3.5	3.0
Anxiety/depression	1.0	1.0	3.5	2.0
R-PAct	N=52	N=15	N=3	N=1
Comb hair	2.0	2.0	2.0	2.0
Eat	2.0	2.0	2.0	2.0
Put on trousers	2.0	1.0	1.0	2.0
Prepare meal	2.0	2.0	1.0	2.0
Take shower	2.0	2.0	1.0	2.0
Reach for an object above the head	2.0	2.0	1.0	2.0
Step over obstacles	1.0	1.0	1.0	2.0
Turnover in bed	1.0	1.0	1.0	2.0
Walk on uneven surfaces	1.0	1.0	1.0	2.0
Stand up from a sitting position	1.0	1.0	1.0	1.0
Walk more than 1 km	1.0	1.0	0.0	1.0
Walk up and down stairs	1.0	1.0	1.0	0.0
Bend over and stand up	1.0	0.0	1.0	0.0
Walk at rapid speed	1.0	0.0	0.0	0.0
Carry out tasks in yard	1.0	0.0	0.0	0.0
Practice a sport	0.0	0.0	0.0	0.0
Squat and stand up	0.0	0.0	1.0	0.0
Run	0.0	0.0	0.0	0.0

EQ-5D-5L: 1, no problems (green); 2, slight problems (yellow); 3, moderate problems (yellow); 4, severe problems (red); 5, unable/extremely (red)
R-PAct: 2, able to (green); 1, able to, with difficulties (yellow); 0, unable to (red)

- Both patients and HCPs found the health state descriptions accurate. The following changes were made:
  - Added statements about dependence on others, balance/falling, urinary difficulties, frustration
  - Removed statements about ability to exercise
  - Adjusted impact of anxiety/depression, fatigue/sleep, social functioning.

Health state utility valuation

- The health states were evaluated by 100 members of the UK general public.
- The UK sample was 42.9 (SD=17.7) mean years old, 51% male and similar to the UK general public in age, gender and ethnicity (UK census 2011).
- EQ-5D-5L mean index scores of the health states ranged from HS1: 0.608 (SD=0.12) to HS7: −0.078 (SD=0.22), and TTO mean weights ranged from HS1: 0.754 (SD=0.31) to HS7: −0.132 (SD=0.50; **Figure 3**).

Figure 3. Mean (95% CI) EQ-5D-5L index scores (top) and TTO weights (bottom); N=100
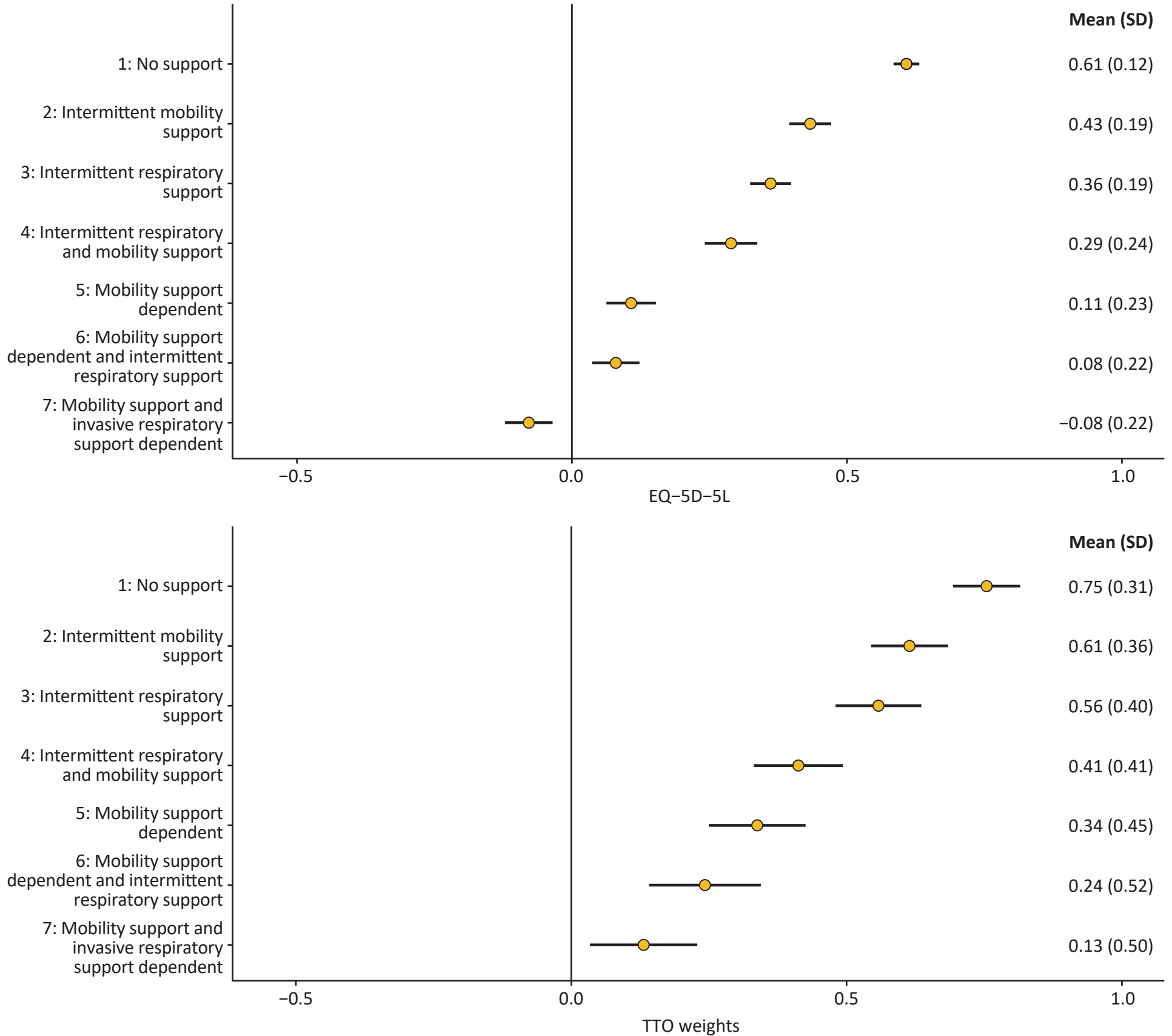
- TTO and EQ-5D-5L results showed a similar pattern, though EQ-5D-5L index scores were consistently lower. Both methods yielded values worse than death for the most advanced clinical presentations, stressing the severity of more progressed LOPD.

DISCUSSION

- This study applied a more robust method for developing health state vignettes by using validated PRO data to support the content validity of the vignettes.
- Use of PRO data meant that the content was driven by LOPD patients using validated measures.
- The vignettes were subsequently refined in extensive qualitative interviews and finalised for a valuation exercise to estimate utilities of different health states of LOPD.
- Estimated utility values highlight the progressive nature of the disease with increased dependence on assistive technology.

POTENTIAL STUDY LIMITATIONS

- Potential limitations of the study are that (1) health states were drafted for symptomatic patients indicated for treatment and the values may not be representative of the general LOPD patient population, and (2) vignettes are a simplification of the burden and cannot represent the full variability of the disease.

CONCLUSIONS

- We believe that supporting vignette development with PRO data represents a significant improvement on standard methods of vignette development and should improve utility estimation in rare diseases.
- The method could be usefully corroborated with additional evidence (literature and qualitative) to cover all HRQL dimensions and all health states.

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