Received: 2 December 2020 | Revised: 13 January 2021 | Accepted: 8 February 2021

DOI: 10.1111/hae.14278

Haemophilia WILEY

ORIGINAL ARTICLE

Clinical haemophilia

Evidence of a disability paradox in patient-reported outcomes in haemophilia

Jamie O'Hara[1,2] | Antony P. Martin[1] | Diane Nugent[3] | Michelle Witkop[4] | Tyler W. Buckner[5] | Mark W. Skinner[6,7] | Brian O'Mahony[8,9] | Brendan Mulhern[10] | George Morgan[1] | Nanxin Li[11] | Eileen K. Sawyer[11]

[1]HCD Economics, Daresbury, UK

[2]Faculty of Health and Social Care, University of Chester, Chester, UK

[3]Department of Pediatrics and Division of Hematology at CHOC Children's Hospital, Center for Inherited Blood Disorders, Orange, CA, USA

[4]National Hemophilia Foundation, New York, NY, USA

[5]Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora, CO, USA

[6]Institute for Policy Advancement, Ltd, Washington, DC, USA

[7]McMaster University, Hamilton, ON, Canada

[8]Irish Haemophilia Society, Dublin, UK

[9]Trinity College, Dublin, UK

[10]Centre for Health Economics Research and Evaluation, University of Technology Sydney, Sydney, NSW, Australia

[11]uniQure Inc, Lexington, MA, USA

Correspondence
George Morgan, HCD Economics, Daresbury, WA4 4FS, UK.
Email: george.morgan@hcdeconomics.com

Funding information
uniQure Inc.

Abstract

Introduction: People with inherited and long-term conditions such as haemophilia have been shown to adapt to their levels of disability, often reporting better quality of life (QoL) than expected from the general population (the disability paradox).

Aim: To investigate the disability paradox in people with haemophilia in the United States by examining preference differences in health state valuations versus the general population.

Methods: We conducted a discrete choice experiment including duration to capture valuations of health states based on patient-reported preferences. Participants indicated their preferences for hypothetical health states using the EQ-5D-5L, where each participant completed 15 of the 120 choice tasks. Response inconsistencies were evaluated with dominated and repeated scenarios. Conditional-logit regressions with random sampling of the general population responses were used to match the sample of patients with haemophilia. We compared model estimates and derived preferences associated with EQ-5D-5L health states.

Results: After removing respondents with response inconsistencies, 1327/2138 (62%) participants remained (177/283 haemophilia; 1150/1900 general population). Patients with haemophilia indicated higher preference value for 99% of EQ-5D-5L health states compared to the general population (when matched on age and gender). The mean health state valuation difference of 0.17 indicated a meaningful difference compared to a minimal clinically important difference threshold of 0.07. Results were consistent by haemophilia type and severity.

Conclusion: Our findings indicated the presence of a disability paradox among patients with haemophilia, who reported higher health states than the general population, suggesting the impact of haemophilia may be underestimated if general population value sets are used.

KEYWORDS
cost-effectiveness, haemophilia, health equity, patient-reported outcome measurement, quality of life

1 | BACKGROUND

Haemophilia is a lifelong genetic disorder associated with significant clinical burden driven by haemarthrosis, joint damage and pain, with subsequent negative impact on patients' mental health, daily functioning and overall quality of life (QoL).[1,2] The substantial reductions in morbidity and mortality afforded by modern therapeutic advances have elevated the aims of haemophilia treatment to realize a functional cure and to bring health equity to patients with this persistent, lifelong condition.[3] As such, the landmark improvements in clinical effectiveness have increased the importance of patient-centric outcomes related to well-being, functionality, and QoL.[4-7] Measuring the patient-reported impact of conditions with lasting disabilities, such as haemophilia, may include a counterintuitive phenomenon known as the 'disability paradox', where patients report good or excellent QoL while observers characterize the patients' daily struggles much less favourably.[8] This disease state adaptation is believed to derive from a re-prioritization of values, a recalibration of essential needs and/or a re-conceptualization of central beliefs as patients adapt to the effects of their condition.[8,9] Importantly, this can cause an underestimation of disease burden and an under-valuation of treatment effects in patient-reported outcomes research.

The QoL of an individual can be derived from preference-based measures of health such as the EuroQoL 5-Dimensions (EQ-5D).[10] The EQ-5D includes five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Once the questionnaire is completed, a health state valuation (HSVs) can be generated using a scoring algorithm designed to be a cardinal index of utility anchored on full health (1) and death (0). Values generated provide a 'utility value set' for each state described by the classification system.[11]

Discrete choice experiments (DCE) are widely used to estimate HSVs. DCEs are an ordinal choice-based method, which assume that people generally choose the option that provides them with the highest level of utility.[12] In DCEs, respondents are typically asked to choose between choice tasks consisting of health scenarios. Each scenario consists of attributes and severity levels for each attribute, and as such, DCE methods may be applied to generate utility value sets. DCEs incorporating an attribute for duration (time trade-off; DCE_{TTO}) can be used to compare value sets by different respondent groups.

It has been suggested that patients with haemophilia rate their health states higher than the general population in some scenarios, but this has not been thoroughly explored or quantified.[13,14] We conducted a DCE_{TTO} using the EQ-5D-5L to investigate the potential of a disability paradox among patients with haemophilia. Using discrete choice methods allowed us to assess self-reported preferences for incremental health state scenarios that can be compared between patients and otherwise healthy peers to characterize differences attributable to disease.[12] We also quantified differences in reported health state valuations between patients with haemophilia and a representative sample of the US general population. Our aim was to identify and characterize the need for adjustments in the evaluation of patient-reported burden of haemophilia and effects of treatment on functionality and QoL.

2 | Methods

2.1 | Study design

In this study, a DCE_{TTO} was designed to present individuals with hypothetical health states (known as 'choice sets') and ask them to choose among a number of alternatives (or 'attributes'). The choice sets presented each of the five dimensions of the preference-based measure EQ-5D-5L and one duration attribute, as described in Table 1. Each dimension (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) had five ordinal levels of severity (none, slight, moderate, severe, extreme/unable). The duration attribute contained five levels (3, 5, 7, 10 and 12 years) to investigate preferences with respect to both their dimensions and potential durations.[15]

TABLE 1 Example of a hypothetical choice task used in the DCE design

	Health description A	Health description B
Mobility	I have no problems in walking about	I have slight problems in walking about
Self-Care	I have no problems washing or dressing myself	I have no problems washing or dressing myself
Usual Activities	I have severe problems doing my usual activities	I have no problems doing my usual activities
Pain/Discomfort	I have slight pain or discomfort	I have no pain or discomfort
Anxiety/Depression	I am extremely anxious or depressed	I am not anxious or depressed
Duration	You live in this health state for 5 years and then you die	You live in this health state for 10 years and then you die
Which scenario do you think is better?	☐	☒

The sum of all possible dimension and duration levels yielded a total of more than 240 million potential choice sets; therefore, a subset of choice sets was generated by maximizing D-efficiency using Ngene software.[16] D-efficiency is used to achieve optimal efficiency in DCEs by maximizing the information gained from a subset of choice sets while minimizing error.[17] The design included 120 choice sets based on D-efficient design using the modified Fedorov algorithm.[18]

Each respondent completed 15 choice sets for the survey. This included 13 choice sets randomly selected for each respondent from the DCE design of 120 choice sets. Two more choice sets were included as quality check measures. A repeated choice set was presented with one of the 13 choice sets being repeated in the exercise. A dominated choice set was where one of the scenarios had unambiguously worse levels for each attribute of the EQ-5D-5L than the other scenario.[19]

2.2 | Study population, setting & study size

Between July and September 2019, adult patients with haemophilia (PwH), caregivers of PwH and a representative sample of the English-speaking US general population (GP) in terms of age, gender and region were recruited via a market research panel. We recruited 250 PwH and 2000 general population respondents.[20] The target sample size represented a trade-off between the desire for accurate estimates (one that reflects the average preferences for PwH) and the practical consideration that haemophilia is a rare disease. The survey was conducted via a secure online portal. We first conducted a pilot study to evaluate participant comprehension of the choice set tasks and the survey functionality. The pilot study included a 10% subset of 200 GP, 25 PwH and 25 caregivers. We also assessed the duration attribute in the DCE_{TTO} design to compare shorter (3, 5, 7, 10 and 12 years) and longer durations (10, 12, 15, 17 and 20 years) using the reliability tests of repeated and dominated scenarios. Shorter duration performed better and was selected for the research.

Upon entering the portal, participants were introduced to the study and had to provide informed consent in order to continue. Baseline demographic data were then collected before the participants were presented with the DCE_{TTO} tasks. Informed consent was obtained from all participants, and the study was conducted in accordance with Declaration of Helsinki. Institutional Review Board (IRB) exemption was determined by the New England IRB.

2.3 | Analysis

The primary analyses compared responses from PwH and the GP. We also collected responses from caregivers of PwH; however, many caregivers had haemophilia themselves and thus were not included in the analyses to avoid confounding. To reduce uncertainty around the heterogeneity between cohorts, only male PwH were included and the age distribution was matched between the GP and PwH. Age matching was achieved by random sampling of the GP to match the PwH proportions by age group and was repeated five times to increase the robustness of resampling for multiple subgroups. The results from the resampling were then aggregated to generate mean values from random sampling responses.

Data were then modelled using conditional-logit regressions to produce an adjusted value set for PwH and the GP.[12] The utility value sets were examined for inconsistencies and ordering was imposed for transitivity. Therefore, any preceding attributes were equal than or less than the current attribute, for example if level 2 of an attribute was greater than the utility of level 1, the two levels would be merged. This method has been commonly used to ensure the applicability of the DCE results.[21] Models for PwH and the GP were compared to test whether the models were on the same scale using a likelihood ratio statistic (LR). An LR test posed the null hypothesis that the PwH and GP models had preference homogeneity. If the LR statistic was above a critical value (calculated as the difference between the number of parameters in both models), then the null hypothesis was rejected, and the difference was considered statistically significant.

From the adjusted value sets generated for PwH and GP, we estimated values for every possible EQ-5D-5L state. Two utilities for each population (PwH and GP) were compared for the average utility difference across health states and the frequency of the average utility were valued higher or lower. Analyses were also conducted for subgroups including by haemophilia type (A and B) and severity (severe and moderate; the sample size for patients with mild haemophilia was too small for robust analyses). All analyses were performed using Stata 16 (StataCorp).

3 | RESULTS

3.1 | Sample

Of the 2183 participants that completed the DCE, 856 (39.2%; 106 [4.9%] PwH and 750 [34.4%] GP) respondents indicated inconsistencies based on the reliability tests and were excluded from the analyses. A total of 1327 participants remained (1150 GP and 177 PwH, including 118 PwHA and 59 PwHB). Demographic characteristics were generally similar between PwH and the GP except that more patients from the GP than PwH were ≥55 years of age (31% vs 11%; $p < .001$), and more PwH were men (77% vs 49%; $p < .001$; Table 2); therefore, sex and age matching were applied for the analyses.

3.2 | Comparison of PwH and the GP

PwH were found to provide higher values for 98.9% of EQ-5D-5L states compared to the GP (Table 3). Figure 1 presents the relative utility values, which illustrates that PwH value states were consistently higher than GP value states with a utility value of 0.9 or less.

TABLE 2 Characteristics for participants included in the analysis

Characteristics	People with haemophilia			General population	*p*-Value (PwH vs GP)
	Type A (*n* = 94)	Type B (*n* = 46)	Total (*n* = 140)	Total (*n* = 562)	
Age (y), mean ± SD	36.7 ± 11.9	34.1 ± 10.5	35.9 ± 11.5	46.3 ± 15.6	<.001
Age groups (y), *n* (%)					
18–34	52.1 (52.1)	28 (60.9)	77 (55.0)	158 (28.1)	<.001
35–54	35 (37.2)	14 (30.4)	49 (35.0)	220 (39.2)	.367
>55	10 (10.6)	4 (8.7)	14 (10.0)	184 (32.7)	<.001
Race, *n* (%)					
White	75 (79.8)	33 (71.7)	108 (77.1)	433 (77.1)	.981
Black African American	9 (9.6)	6 (13.0)	15 (10.7)	59 (10.5)	.941
American Indian/ Alaskan Native	1 (1.1)	0 (0)	1 (0.7)	6 (1.1)	.707
Asian	4 (4.3)	3 (6.5)	7 (5.0)	28 (5.0)	.993
Hawaiian/Pacific	1 (1.1)	0 (0)	1 (0.7)	3 (0.5)	.800
Other	4 (4.3)	3 (6.5)	7 (5.0)	28 (5.0)	.993
Not stated	0 (0)	0 (0)	1 (0.7)	5 (0.9)	.840
Region, *n* (%)					
Northeast	16 (17.0)	4 (8.7)	20 (14.3)	71 (12.6)	.603
Midwest	26 (27.7)	11 (23.9)	37 (26.4)	113 (20.1)	.103
South	34 (36.2)	21 (45.7)	55 (39.3)	189 (33.6)	.209
West	18 (19.2)	10 (21.7)	28 (20.0)	189 (33.6)	.002
Chronic comorbidities, *n* (%)					
Any	94 (100)	46 (100)	140 (100)	287 (51.1)	<.001
Haemophilia	94 (100)	46 (100)	140 (100)	0 (0)	<.001
Tiredness/fatigue	7 (7.5)	9 (19.6)	16 (11.4)	49 (17.1)	.127
Pain	21 (22.3)	9 (19.6)	30 (21.4)	92 (32.1)	.022
Insomnia	4 (4.3)	8 (17.4)	12 (8.6)	36 (12.5)	.223
Anxiety/nerves	14 (14.9)	10 (21.7)	24 (17.1)	63 (22.0)	.247
Depression	16 (17.0)	10 (21.7)	26 (18.6)	82 (28.6)	.026
Diabetes	6 (6.4)	0 (0)	6 (4.3)	59 (20.6)	<.001
Breathing problems	6 (6.4)	4 (8.7)	10 (7.1)	52 (18.1)	.003
Heart disease	0 (0)	0 (0)	0 (0)	32 (11.2)	<.001
High blood pressure	16 (17.0)	3 (6.5)	19 (13.6)	111 (38.7)	<.001
Osteoarthritis	14 (14.9)	3 (6.5)	17 (12.1)	26 (9.1)	.320
Stroke	1 (1.1)	1 (2.2)	2 (1.4)	5 (1.7)	.811
Cancer	1 (1.1)	0 (0)	1 (0.7)	11 (3.8)	.067
Other	4 (4.3)	7 (15.2)	11 (7.9)	108 (37.6)	<.001

Abbreviations: GP, General Population; *N*, number; PwH, People with Haemophilia; SD, standard deviation; Y, year.

The mean HSV difference between PwH and the GP was 0.17 across all possible EQ-5D-5L states. An approximation of the minimal clinically important difference (MCID) for the EQ-5D-5L based on EQ-5D-3L values was used as EQ-5D-5L US MCIDs are not available; therefore, the MCID is reported as 0.07[22] indicating that the HSV difference between PwH and the GP was clinically meaningful. LR tests also showed that the two utility scales differed significantly between responses from PwH and the GP (LR = 36.34; $p < .01$).

EQ-5D-5L individual attribute mean utility values are illustrated in Figure 2. The results indicated that mobility and self-care attributes were associated with a greater impact on QoL for PwH across all five levels of severity.

3.3 | Subgroup analysis of haemophilia type and severity

For PwHA and PwHB, utility valuations were found to be higher for 96.5% and 97.4% of EQ-5D-5L states compared to valuations by the GP (Table 3), respectively. Figure S1 presents the relative utility

TABLE 3 Comparative EQ-5D-5L value sets by haemophilia type and severity.

	PwH vs GP	PwHA vs GP	PwHB vs GP	PwSH vs GP	PwMH vs GP
Comparison of the utility scores:					
PWH > GP, *n* (%)	3091 (98.91)	3017 (96.54)	3043 (97.38)	2982 (95.42)	3089 (98.85)
GP > PWH, *n* (%)	33 (1.06)	107 (3.42)	81 (2.59)	142 (4.54)	35 (1.12)
No difference, *n* (%)	1 (0.03)	1 (0.03)	1 (0.03)	1 (0.03)	1 (0.03)
Difference in utility score (PWH vs GP):					
Mean (SD)	0.17 (0.08)	0.17 (0.10)	0.21 (0.11)	0.14 (0.09)	0.17 (0.08)
Median (IQR)	0.17 (0.11)	0.17 (0.10)	0.21 (0.17)	0.14 (0.13)	0.16 (0.11)

Abbreviations: EQ-5D-5L, EuroQol-5-dimensions 5-level; GP, general population; IQR, interquartile range; *N*, number; PwHA, people with haemophilia A; PwHB, people with haemophilia B; PwMH, people with moderate haemophilia; PwSH, people with severe haemophilia; SD, standard deviation; Y, year.

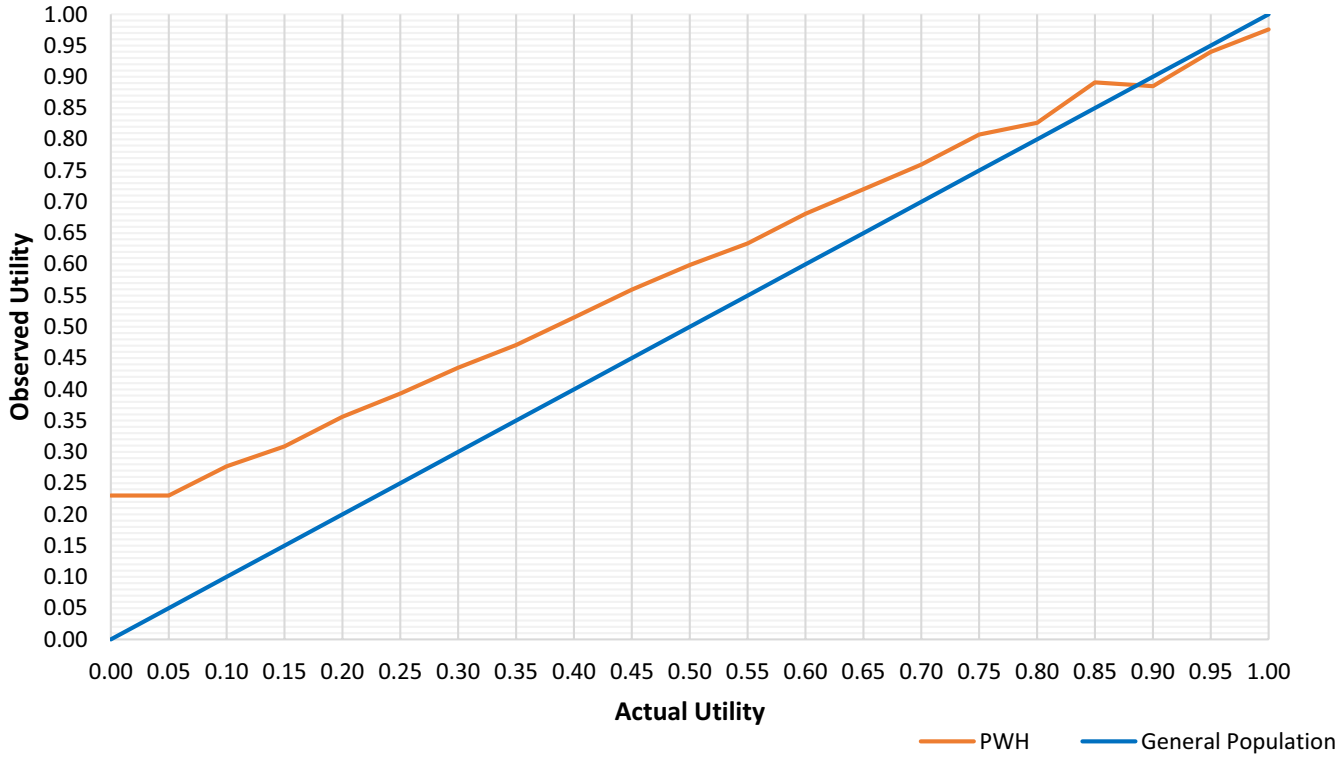

FIGURE 1 Graphical representation of observed utility of PwH compared to actual utility. Abbreviations: PwH, people with haemophilia. Note: Actual utility describes the utility that was observed by the general population. Observed utility describes the corresponding utility that was elicited from PwH. Based on utility decrements derived from the DCE_{TTO} for the EQ-5D-5L across 3125 states, corresponding health state utility values were derived. Using 0.05 utility intervals, based on health state utility values derived from the general population, corresponding values derived from PwH were plotted. For each 0.05 interval and utility value reported by the general population, the corresponding utility value weighted average was described [Colour figure can be viewed at wileyonlinelibrary.com]

values of PwHA and PwHB compared to GP. The mean HSV difference was 0.17 (PwHA) and 0.21 (PwHB) relative to the GP, both exceeding the MCID of the EQ-5D-5L. LR tests also showed that the utility scales differed significantly between responses from PwHA and the GP (LR = 33.08; $p < .001$) and PwHB and GP (LR = 30.44; $p < .01$).

For people with severe haemophilia (PwSH) and people with moderate haemophilia (PwMH), utility valuations were found to be higher for 95.4% and 98.9% of EQ-5D-5L states compared to valuations by the GP (Table 3), respectively. Figure S2 presents the relative utility values of PwSH and PwMH compared to the GP. The mean HSV difference was 0.14 (PwSH) and 0.17 (PwMH) relative to the GP, both exceeding the MCID of the EQ-5D-5L. LR tests also showed that the utility scales differed significantly between responses from PwSH and the GP (LR = 31.32; $p < .01$); however, this was not seen for PwMH and GP (LR = 11.77; $p = .4645$).

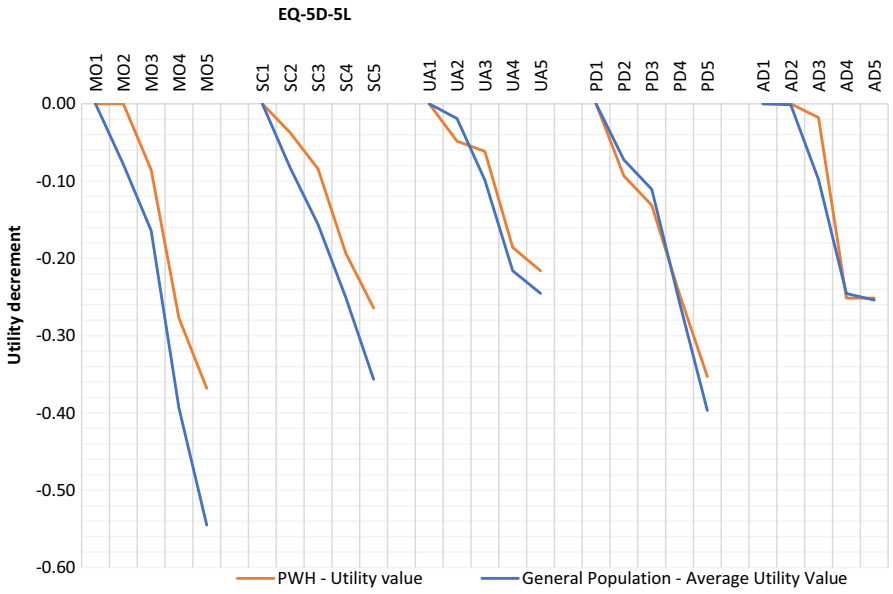

FIGURE 2 Graphical representation of the EQ-5D-5L coefficients for PwH and GP. Abbreviations: MO, Mobility; SC, Self-Care; UA, Usual Activities; PD, Pain and Discomfort; AD, Anxiety and Depression; PwH; people with haemophilia. Notes: By domain, the levels of responses range from no problems to severe problems (1–5) [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

Our study revealed evidence of the disability paradox in haemophilia patient-reported outcomes, where people with haemophilia reported significantly higher health state valuations than otherwise healthy peers from the general US population. This difference was both statistically significant and clinically meaningful, with consistent results across haemophilia A and B as well as severe and moderate patients. These findings should be considered in the design and interpretation of patient-reported outcomes research in haemophilia.

Our findings are consistent with studies of disease state adaptation reported in haemophilia and other chronic conditions, where patients have reported higher health states than otherwise healthy peers.[23-25] A recent patient preference study by Carlsson et al. (2017)[25] showed that patients with haemophilia A consistently rated their health states higher than their peers in the GP (score range, 0.67–0.73 for PwHA vs 0.54–0.60 for the GP). Our study indicated a disability paradox in PwH using a validated, widely used QoL instrument, the EQ-5D-5L. Our application of the composite DCE_{TTO} method to include consideration of the duration of health states offers a robust approach not only to test for the existence of the disability paradox, but also to quantify its impact. Gandhi and colleagues (2017)[23] observed that patients with heart disease or cancer reported similar health state utility values as the general population when adjusted for sociodemographic characteristics. Peeters and Stiggelbout (2010)[24] conducted a meta-analysis showing that patients across a variety of conditions generally provided higher health state valuations than 'non-patients' from the GP. Alternatively, similar health state valuations have been reported between patients with epilepsy and healthy peers, and worse ratings for those with dementia compared to the GP.[26,27] In the context of this broader heterogeneity, our findings support the use of haemophilia-specific health utility assessments for the accurate design and interpretation of patient-centric research.

Our work has implications for clinical research assessments and for broader population health management and policy decisions. In the pursuit of greater health equity for people with haemophilia, patient-centric outcome measures are used more often and with greater consideration. We observed and quantified a disability paradox in PwH-rated health states using the EQ-5D-5L. The frequent use of this instrument in clinical research and health technology assessments emphasizes the likelihood that disease burden is underestimated and treatment effect is under-valued when the disease state adaptation is not factored into totality of treatment benefits and health technology evaluations. As novel treatment options such as gene therapy emerge with the potential to approach a functional cure,[28,29] the characterization of patient-centric value should account for the 'true' burden of haemophilia and relative improvements offered by new therapeutic strategies.

This study should also be considered in the context of certain strengths and limitations. We utilized the validated EQ-5D-5L for patient-reported outcomes, which should offer some generalizability to future research efforts using the same instrument. The DCE and time trade-off methods are common in health services research. Since the DCE_{TTO} was completed online, without an in-person facilitator to guide the respondent through the activity, there may have been some impact on the accuracy of responses if a participant did not fully understand a given question[30]; however, we sought to account for this potential limitation by removing inconsistent responses in the analysis. Due to haemophilia being a rare condition, we were limited by sample size in our subgroup analysis; future research could address these subgroups with a larger sample size to see if the findings hold true. Unobserved patient characteristics and contextual factors may have contributed to the heterogeneity of reported preferences. Further research may account for additional observable characteristics that may differ between cohorts, such as the presence of comorbidities or additional sociodemographic considerations.

5 | CONCLUSION

Our findings indicated the presence of a disability paradox in the population preferences for haemophilia. Clinical and health technology assessments should account for health state-derived QoL evaluations specific to people with haemophilia. The unmet needs identified in current standards of care are likely to underestimate the burden of haemophilia on patients and caregivers, and standard QoL instruments that do not account for the disability paradox may not be accurate for clinical assessments and health policy decisions.

ACKNOWLEDGEMENTS

The authors thank Gabriel Pedra, Sohaib Asghar and Thomas Burke for their time and effort with statistical support and interpretation of the results. Medical writing support was provided by Jeff Frimpter, MPH, of HCD Economics, supported by uniQure Inc.

CONFLICT OF INTEREST

JOH, APM and GM work for HCD Economics who were funded by uniQure Inc. to undertake this research. EKS and NL are employees of uniQure Inc. DN, MW, BM, TB, MS and BOM have no interests to declare.

AUTHOR CONTRIBUTIONS

APM and JOH contributed to the concept and design. APM, JOH and GM performed the research. APM, JOH, GM, BM, NL and EKS analysed the data. All authors contributed to the interpreting the data and the writing of the paper.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Michelle Witkop https://orcid.org/0000-0003-0758-286X
Mark W. Skinner https://orcid.org/0000-0002-0934-0680
George Morgan https://orcid.org/0000-0003-2014-3415

REFERENCES

1. Witkop ML, Lambing A, Nichols CD, Munn JE, Anderson TL, Tortella BJ. Interrelationship between depression, anxiety, pain, and treatment adherence in hemophilia: results from a US cross-sectional survey. *Patient Prefer Adherence*. 2019;13:1577-1587. https://doi.org/10.2147/PPA.S212723
2. Witkop M, Neff A, Buckner TW, et al. Self-reported prevalence, description and management of pain in adults with haemophilia: methods, demographics and results from the Pain, Functional Impairment, and Quality of life (P-FiQ) study. *Haemophilia*. 2017;23(4):556-565. https://doi.org/10.1111/hae.13214
3. Skinner MW, Nugent D, Wilton P, et al. Achieving the unimaginable: Health equity in haemophilia. *Haemophilia*. 2020;26(1):17-24. https://doi.org/10.1111/hae.13862
4. van Balen EC, Gouw SC, Hazelzet JA, van der Bom JG, Cnossen MH. Defining patient value in haemophilia care. *Haemophilia*. 2018;24(4):516-518. https://doi.org/10.1111/hae.13550
5. O'Mahony B, Dolan G, Nugent D, Goodman C. Patient-centred value framework for haemophilia. *Haemophilia*. 2018;24(6):873-879. https://doi.org/10.1111/hae.13456
6. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. *Health Technol Assess*. 2001;5(4):1-157. https://doi.org/10.3310/hta5040
7. Fischer K, Nijdam A, Holmström M, et al. Evaluating outcome of prophylaxis in haemophilia: objective and self-reported instruments should be combined. *Haemophilia*. 2016;22(2):e80-e86. https://doi.org/10.1111/hae.12901
8. Albrecht GL, Devlieger PJ. The disability paradox: high quality of life against all odds. *Soc Sci Med*. 1999;48(8):977-988. https://doi.org/10.1016/s0277-9536(98)00411-0
9. Schwartz CE, Andresen EM, Nosek MA, Krahn GL. Response shift theory: important implications for measuring quality of life in people with disability. *Arch Phys Med Rehabil*. 2007;88(4):529-536. https://doi.org/10.1016/j.apmr.2006.12.032
10. Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *Eur J Heal Econ*. 2018;19(1):123-152. https://doi.org/10.1007/s10198-017-0871-0
11. Mulhern B, Norman R, Street DJ, Viney R. One method, many methodological choices: a structured review of discrete-choice experiments for health state valuation. *Pharmacoeconomics*. 2019;37(1):29-43. https://doi.org/10.1007/s40273-018-0714-6
12. Mcfadden D. Conditional Logit Analysis of Qualitative Choice Behavior. *Zaremb*. New York, NY: Academic Press; 1974.
13. Grosse SD, Chaugule SS, Hay JW, Disabilities D, Angeles L. Estimates of utility weights in hemophilia: implications for cost- utility analysis of clotting factor prophylaxis. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(2):267-283. https://doi.org/10.1586/14737167.2015.1001372.Estimates
14. Hoxer CS, Zak M, Benmedjahed K, Lambert J. Utility valuation of health states for haemophilia and related complications in Europe and in the United States. *Haemophilia*. 2019;25(1):92-100. https://doi.org/10.1111/hae.13634
15. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual life Res an Int J Qual life Asp Treat care Rehabil*. 2011;20(10):1727-1736. https://doi.org/10.1007/s11136-011-9903-x
16. de Bekker-Grob EW, Donkers B, Jonker MF, Stolk EA. Sample size requirements for discrete-choice experiments in healthcare: a practical guide. *Patient*. 2015;8(5):373-384. https://doi.org/10.1007/s40271-015-0118-z
17. Reed Johnson F, Lancsar E, Marshall D, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. *Value Health*. 2013;16(1):3-13. https://doi.org/10.1016/j.jval.2012.08.2223
18. Cook RD, Nachtsheim CJ. A comparison of algorithms for constructing exact D-optimal designs. *Technometrics*. 1980;22(3):315-324. https://doi.org/10.2307/1268315
19. Mattmann M, Logar I, Brouwer R. Choice certainty, consistency, and monotonicity in discrete choice experiments. *J Environ Econ Policy*. 2019;8(2):109-127. https://doi.org/10.1080/21606544.2018.1515118
20. Pearmain D, Kroes EP, Hague Consultancy Group. In *Stated Preference Techniques: A Guide to Practice*. Richmond, Surrey: Steer Davies & Gleave Ltd; 1990.
21. Rowen D, Mulhern B, Stevens K, Vermaire JH. Estimating a Dutch value set for the pediatric preference-based CHU9D using a discrete choice experiment with duration. *Value Health*. 2018;21(10):1234-1242. https://doi.org/10.1016/j.jval.2018.03.016

22. Coretti S, Ruggeri M, McNamee P. The minimum clinically important difference for EQ-5D index: a critical review. *Expert Rev Pharmacoeconomics Outcomes Res*. 2014;14(2):221-233. https://doi.org/10.1586/14737167.2014.894462
23. Gandhi M, Tan RS, Ng R, et al. Comparison of health state values derived from patients and individuals from the general population. *Qual Life Res*. 2017;26(12):3353-3363. https://doi.org/10.1007/s11136-017-1683-5
24. Peeters Y, Stiggelbout AM. Health state valuations of patients and the general public analytically compared: a meta-analytical comparison of patient and population health state utilities. *Value Health*. 2010;13(2):306-309. https://doi.org/10.1111/j.1524-4733.2009.00610.x
25. Steen Carlsson K, Andersson E, Berntorp E. Preference-based valuation of treatment attributes in haemophilia A using web survey. *Haemophilia*. 2017;23(6):894-903. https://doi.org/10.1111/hae.13322
26. Rowen D, Mulhern B, Banerjee S, et al. Comparison of general population, patient, and carer utility values for dementia health states. *Med Decis Mak*. 2015;35(1):68-80. https://doi.org/10.1177/0272989X14557178
27. Brazier JE, Dixon S, Ratcliffe J. The role of patient preferences in cost-effectiveness analysis: a conflict of values? *Pharmacoeconomics*. 2009;27(9):705-712. https://doi.org/10.2165/11314840-000000000-00000
28. Nathwani AC. Gene therapy for hemophilia. *Hematol Am Soc Hematol Educ Progr*. 2019;2019(1):1-8. https://doi.org/10.1182/hematology.2019000007
29. HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03569891. Accessed May 12, 2020.
30. Determann D, Lambooij MS, Steyerberg EW, de Bekker-Grob EW, de Wit GA. Impact of survey administration mode on the results of a health-related discrete choice experiment: online and paper comparison. *Value Health*. 2017;20(7):953-960. https://doi.org/10.1016/j.jval.2017.02.007

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: O'Hara J, Martin AP, Nugent D, et al. Evidence of a disability paradox in patient-reported outcomes in haemophilia. *Haemophilia*. 2021;27:245–252. https://doi.org/10.1111/hae.14278