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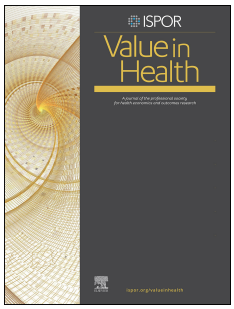

Development and testing the psychometric properties of 20 bolt-on items for the EQ-5D-5L across 31 rare diseases

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Precis: This study developed and tested the psychometric properties of 20 bolt-on items for the EQ-5D-5L in a nationwide sample of patients with rare diseases in China.

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Abstract

Objective: Our objective was to develop and assess the psychometric properties of relevant bolt-on items for the EQ-5D-5L in patients with rare diseases (RDs).

Methods: Nineteen new EQ-5D-5L bolt-ons were developed based on literature review, expert input and qualitative interviews and focus groups with patients, caregivers and representatives of patient associations. A nationwide, cross-sectional, web-based survey in China included patients or caregivers of patients with 31 RDs in China (n=9,190). In each RDs, participants completed the EQ-5D-5L and three out of 20 [one existing and 19 newly-developed] bolt-ons. Ceiling, explanatory power, convergent, divergent and known-group validity were examined.

Results: Among the bolt-ons, itching had the lowest ceiling (6.5%), while social relationships had the highest (42.2%). The absolute reduction in the ceiling of the EQ-5D-5L with the addition of any bolt-ons was limited, ranging from 0 (respiratory problems) to 8.3%-points (isolation). Dignity and vitality resulted in the largest increase in explained variance in EQ VAS. The isolation, fertility and visual acuity bolt-ons showed good divergent validity from the EQ-5D-5L items. There was strong convergent validity between SF-12 and conceptually-related bolt-ons (e.g., physical health composite and muscle problems bolt-on). Various bolt-ons improved the known-groups validity in specific patient groups, e.g., Huntington's disease (oral expressions),

scleroderma (dexterity), myasthenia gravis (muscle problems), neuromyelitis optica and multiple sclerosis (fatigue), Marfan syndrome (self-image) and Pompe disease (safety).

Conclusion: The EQ-5D-5L shows sufficient validity in most RDs, but incorporating relevant specific bolt-ons could enhance its ability to more comprehensively assess health-related quality of life in these patients.

Key words: EQ-5D-5L; psychometric properties; bolt-on; rare diseases; health-related quality of life

Highlights

- Generic preference-based measures, such as the EQ-5D may not fully capture the symptoms and disabilities experienced by people with rare diseases (RDs). Bolt-ons can measure aspects of health-related quality of life not covered by the five core items of the EQ-5D. Although many bolt-ons exist for the EQ-5D, little is known about their value in RDs.
- This study developed and psychometrically tested a set of EQ-5D-5L bolt-ons in RDs using a large, nationwide sample of Chinese patients with 31 RDs. With few exceptions, the addition of bolt-ons to the EQ-5D-5L led to a limited reduction in ceiling. Dignity appears relevant across most RD populations. Isolation, fertility and visual acuity showed the strongest divergent validity. Various bolt-ons enhanced known-group validity of the EQ-5D-5L in specific RDs.
- Our findings provide evidence regarding the usefulness of EQ-5D-5L and associated bolt-on items in comprehensively assessing the health-related quality of life in patients with various RDs. These results can guide future decisions on the development, refinement and selection of bolt-ons for these populations and beyond. The developed bolt-on items may be used in the sensitivity analysis of the reference case EQ-5D-5L and inform resource allocation decisions.

Introduction

The EQ-5D is a widely used preference-based measure of health-related quality of life (HRQoL) in economic evaluations recommended by health technology assessment bodies and pharmacoeconomic guidelines worldwide.[1,2] It allows for the estimation of quality-adjusted life years, which are essential for assessing the value of healthcare interventions. Although the robust psychometric performance of EQ-5D has been demonstrated in various populations,[3] concerns have been raised about its content validity and responsiveness to change in some specific patient groups or clinical settings.[4–6] To address this limitation, the concept of bolt-ons has been introduced. These additional items aim to supplement the core items of the EQ-5D with relevant information for specific (patient) populations, health interventions, or contexts.[7]

Rare diseases (RDs) are medical conditions that affect a small percentage of the population, typically fewer than 1 out of 2000 people.[8] Despite there being more than 10,000 RDs cumulatively, there is limited medical knowledge about their complexities, which hampers effective clinical management.[9] Patients with RDs often experience a significant impact on their HRQoL, including physical limitations, emotional distress, and social isolation.[10] The EQ-5D has been used in some RDs, such as multiple sclerosis,[11] cystic fibrosis,[12] pemphigus,[13] Duchenne muscular dystrophy,[14] Fabry disease,[15] haemophilia,[16] and SMA.[17] However, evidence about its psychometric properties is limited and inconsistent across different diseases and populations.[18]

Developing bolt-on items to the EQ-5D for patients with RDs may be beneficial. Practically, RDs typically present unique and complex symptom patterns that the standard EQ-5D dimensions

may not fully capture.[19] Additionally, the impact of RDs can vary widely even within the same condition, affecting different aspects of HRQoL for different patients.[20] Bolt-on items can help capture this heterogeneity by allowing for the inclusion of aspects relevant to a specific disease. Furthermore, since most RDs lack disease-specific HRQoL instruments, adding bolt-on items to the EQ-5D provide a practical solution to fill this gap, allowing for more comprehensive assessments without the need to develop entirely new instruments. Methodologically, the bolt-on approach also allows comparisons with the general population and any other health conditions as it retains the five core items of the EQ-5D.

Although the addition of bolt-ons to improve the performance of the EQ-5D in the general population or some patient groups has been documented,[21–29] evidence in the context of RDs is limited.[30] Thus, the objective of this study was to develop relevant bolt-ons for the five-level EQ-5D (EQ-5D-5L) and assess their psychometric properties in a large sample of patients with various RDs in China. Due to the low prevalence of RDs, a large country such as China is advantageous, as it can provide the required sample size within a single country.

Methods

The study had two phases. In the first phase, bolt-on items were identified, selected, and developed for 31 RDs, while the second phase tested their psychometric properties in a large nationwide sample in China.

Phase 1: Identification, selection, and development of EQ-5D-5L bolt-on items

The bolt-on development process involved a literature review, expert discussions, and qualitative research with patients, caregivers and representatives of relevant patient associations. This approach ensured that the final selection and wording of bolt-on items genuinely reflected the diverse needs and perspectives of the patients and their respective communities. This process was similar to the bolt-on development criteria published in 2022,[7] although these were unavailable at the time of our development work in 2019.

Overall, 31 RDs were selected for the present study. The bolt-on items were developed in Simplified Chinese language in five steps and aimed to capture both psychosocial and physical HRQoL aspects among individuals with various RDs. First, a core research team conducted a literature review of existing bolt-on items and content from relevant generic and condition-specific measures, both preference and non-preference-based. We also reviewed the literature on patients' experiences with RDs, including symptoms, complications, and treatment side effects. Second, the research team initially created a list of 20 bolt-on items. Subsequently, a diverse panel of 15 experts – specializing in clinical medicine, psychometrics, social work, and public health – was convened. This panel discussed and refined the wording of each item and its response levels. They also offered preliminary recommendations on which bolt-on items are most appropriate for specific RDs. Third, we conducted one-on-one video-interviews with at least one manager, patient, and caregiver from each RD patient association (a total of 35 managers, 31 patients, and 31 caregivers). They were asked to review the complete list of bolt-on items, discuss the suitability of items recommended by experts, and select up to four items that were most relevant for their specific RD. Fourth, the research team conducted 31 focus

groups with patient associations. Each focus group included at least three RD patients or caregivers and a representative from the respective patient association. The primary objective of these focus groups was to further discuss the relevance of the selected bolt-on items and to refine the wording. Finally, after internal discussions within the core research team, the final list of bolt-on items was been agreed upon. Among all the bolt-on items, dignity was identified as crucial for all patients with RDs as it impacts their HRQoL and wellbeing. Thus, dignity was the only bolt-on item tested for all RDs in the next phase of the study. In each RD, two additional bolt-on items were selected in addition to dignity. Some bolt-ons were more generic (e.g., vitality, fatigue), while others were specific to symptoms (e.g., itching, respiratory problems). Moreover, some focused not on HRQoL constructs but on wellbeing (e.g., happiness, safety).

Bolt-on item structure and wording

The final wording of the bolt-ons was developed through an iterative process, incorporating input from each stage of the study. The wording for one bolt-on (dignity) was adopted from our previous hemophilia study[30] without modification, while the remaining 19 bolt-ons were newly developed. We ensured that each bolt-on item's structure aligned with the EQ-5D-5L's format, including a short dimension title and five response levels. Where needed, we added explanations next to the dimension titles for clarity. The response levels were structured with the first level indicating the best status and the last level the worst. Most bolt-on items used the following response format: "I have no... (specific problems)," "I have slight... (specific problems)," "I have moderate... (specific problems)," "I have severe... (specific problems)," and "I have extreme... (specific problems)/unable to do." Deviations were made for some items

where the construct required it; for example, for “dignity” we used “I live with full dignity” and so forth. Both self-complete and proxy 1 (caregiver perspective) versions were developed for all bolt-ons. The exact wording of bolt-on items can be obtained by from the EuroQol Research Foundation.

Phase 2: Cross-sectional survey in 31 RDs

Sample and participants

A nationwide, cross-sectional, and web-based survey was conducted between August 2019 and January 2020 in China. The details of study aims, design, data collection, and project administration can be found in our previous study.[31] In this study, we used data from respondents with all 31 RDs, who were over 15 years old, and completed the EQ-5D-5L along with relevant bolt-on items. If respondents were unable to complete the questionnaire themselves, their primary caregivers were asked to fill out the proxy 1 version.

Survey content

Background characteristics

Information about respondents’ sex (male/female), age (years), employment status (active/non-active), residential registry (urban/rural), family income per year (nine categories ranging from < CNY 5,000 to > CNY 500,001), duration of RD (years, from onset of symptoms to present), number of children (0/1/2/3+), frequency of (using) assistive devices, and history of genetic test (received or not) was collected.

EQ-5D-5L and bolt-ons

The official Simplified Chinese version of the EQ-5D-5L was used in this study. The EQ-5D-5L comprises two sections: a descriptive system and a visual analogue scale (EQ VAS). The descriptive system consists of five dimensions: mobility (MO), self-care (SC), usual activities (UA), pain/discomfort (PD), and anxiety/depression (AD).[32] Each dimension is assessed on a 5-level scale, ranging from "no problems" (1) to "extreme problems/unable to" (5). The EQ VAS reflects a person's overall health on a vertical visual analogue scale, ranging from 0 to 100, with a higher score indicating a better health. No value sets were employed in the present study, however, for known-group validity analyses level sum scores (LSSs) were computed by summarizing the score on each of the five dimensions. After the EQ VAS, all respondents were asked to first complete the "dignity" bolt-on item, followed by two bolt-on items specific to the RD.

The 12-Item Short Form Health Survey (SF-12)

The official Simplified Chinese SF-12, which is a generic measure of HRQoL, which is a shortened version of the SF-36 questionnaire, was used in this study. The SF-12 can generate two scores: a Physical Composite Score (PCS) and a Mental Composite Score (MCS). The scores are normalized on a scale of 0-100, with a mean (SD) PCS or MCS of 50 (10) referring to the general population.[33] A higher composite score indicates better HRQoL.

The Medical Outcome Study Social Support Survey (MOS-SSS)

The official Simplified Chinese MOS-SSS, which is a 19-item questionnaire used to measure the perceived availability of social support in four subscales: emotional/informational, tangible, affectionate, and positive social interaction was used in this study.[34] All items are rated on a five-point scale, ranging from 1, indicating “none of the time”, to 5, meaning “all of the time”. The responses are then added to form an overall summary score. A higher score indicates a greater perception of social support.

Statistical analysis

Analyses were conducted at both the item level and the instrument level (i.e., EQ-5D-5L+bolt-on vs. EQ-5D-5L alone).[30,35] The analyses were performed for the overall sample by individual bolt-on, and wherever possible, also for each RD separately. If the sample size of a RD was fewer than 10, it was removed from certain psychometric analyses (i.e., convergent and known-group validity assessment). Statistical analyses were conducted using STATA software (StataCorp, College Station, Texas, USA). A significance level of $p<0.05$ was used.

Descriptive analysis was used to summarize the patients' sociodemographic and clinical characteristics. Patients' responses on each level of the five EQ-5D-5L and each bolt-on item were presented as frequency (N) and proportion (%). Ceiling and floor were expressed as the proportion of patients reporting no and extreme problems in each item, respectively. At the instrument level, we determined the ceiling for the EQ-5D-5L (proportion of 11111 responses) as well as for the EQ-5D-5L+bolt-on (proportion of 111111 responses). We hypothesized that adding bolt-ons to the descriptive system would reduce the ceiling of the EQ-5D-5L.

A multivariable linear regression analysis was conducted to evaluate the explanatory power of the bolt-on items on EQ VAS. For each bolt-on item, two models were developed, resulting in a total of 40 models. The first model included only the five items of the EQ-5D-5L, while the second model included the five items of the EQ-5D-5L plus the bolt-on item. The difference in adjusted R^2 between the two models was calculated to determine explanatory power of bolt-on items. The bolt-ons were ranked in descending order based on the magnitude of improvement in adjusted R^2 achieved.

Convergent and divergent validity were assessed by examining correlations between the bolt-on items and SF-12, MOS-SSS, the five core items of EQ-5D-5L, and EQ VAS. Spearman's rank correlation (rs) was used to assess the strength of the associations, where rs≥0.5 indicates a strong, rs<0.5 to rs≥0.3 a moderate and rs<0.3 a weak correlation.[36] We hypothesized that bolt-on items measuring physical HRQoL would correlate moderately to strongly with the PCS, while those measuring mental HRQoL would correlate with the MCS of the SF-12, and social HRQoL related bolt-ons would correlate with the MOS-SSS. We also expected certain bolt-on items to moderately or strongly correlate with EQ-5D-5L items (e.g., fear and AD) capturing a conceptually-related construct. Otherwise, weak or no correlations were hypothesized between the bolt-ons and the five core items of the EQ-5D-5L.

We used ANOVA to compare the mean LSSs of the EQ-5D-5L and EQ-5D-5L plus bolt-on item(s) for known-groups of patients defined based on selected clinical characteristics, symptoms or

side-effects (e.g., sunburned skin for albinism, difficulty swallowing for amyotrophic lateral sclerosis, and dysarthria for spinal muscular atrophy). Previous research has confirmed the robust psychometric properties of LSSs, making them a useful outcome for exploratory methodological research.[37,38] Effect size was estimated using Cohen's d (≥0.8 large, 0.50-0.79 medium, 0.20-0.49 small, <0.20 negligible) [36]. The effect sizes for the EQ-5D-5L and the EQ-5D-5L plus each bolt-on were compared for each RD, with a larger effect size (in absolute value) indicating better discriminative power.

Ethical consideration

The study protocol was approved by the Institutional Review Board of the University (Reference ID: SBRE-18-268), and informed consent was obtained from all respondents.

Results

Participant's characteristics

A total of 9,190 patients with 31 RDs completed the questionnaire, including the EQ-5D-5L and specific bolt-on items. Among them, 51.6% were female, approximately 67% were younger than 40 years old (Table 1). The mean EQ VAS score was 58.7 (SD=24.0). Background characteristics for each RD are presented in *Supplementary file 1*. The most prevalent RDs in our sample were myasthenia gravis (n=2164) and hemophilia (n=1158) (Figure 1).

Response distribution and ceiling on EQ-5D-5L and bolt-on items

The distribution of responses for the EQ-5D-5L and bolt-on items is presented in Table 2 for the total sample and in *Supplementary file 2* for each RD. All participants have completed the dignity bolt-on, yet only 20.8% of them expressed that they live in full dignity. The fewest respondents with no problems related to dignity were identified in congenital adrenal hyperplasia (60.7%) and homozygous familial hypercholesterolemia (33.3%), while the lowest percentages were found in Dravet syndrome (0%) and spinocerebellar ataxia (4.4%). Overall, the itching bolt-on showed the lowest ceiling (6.5%), followed by fatigue (7.2%) and isolation (7.3%). The highest ceiling was reported for the social relationships bolt-on (42.2%), followed by dexterity of both hands/fingers (36.3%) and fertility (34.9%). Eleven bolt-ons demonstrated a higher floor than any of the five EQ-5D-5L items. The lowest floor was observed for dexterity of both hands/fingers (1.8%), sleep (1.9%), and social relationships bolt-ons (2.6%), while the highest floor was reported for weight control (39.1%), fertility (32.1%), and self-image (29.6%).

In the total sample, the ceiling for the EQ-5D-5L was small (5.9%), which decreased to 4.0% after adding the dignity bolt-on. The EQ-5D-5L demonstrated the highest ceiling in congenital adrenal hyperplasia (39.3%), albinism (18.8%), and homozygous familial hypercholesterolemia (16.7%). The absolute reduction in ceiling with bolt-ons varied, ranging from 8.3%-points (isolation) to 0%-points (respiratory problems). The highest absolute reduction in ceiling was observed with the self-image bolt-on in congenital adrenal hyperplasia (24.2%-points), the isolation bolt-on in congenital adrenal hyperplasia (21.2%-points), albinism (18.8%-points) and Niemann-Pick disease (11.1%-points), and with fertility in Kallmann syndrome (12.8%-points).

The highest absolute ceiling reduction with the dignity bolt-on was observed in albinism (7.7%-points) and Kallmann syndrome (6.4%-points) and congenital adrenal hyperplasia (6.1%-points).

Explanatory power of bolt-on items

The five EQ-5D-5L dimensions explained 14.1% (osteogenesis imperfecta) to 39.3% (Prader-Willi syndrome) of the variance in EQ VAS scores (Table 3). When adding a bolt-on item to the five EQ-5D-5L items, the largest increase in adjusted R^2 was observed with the dignity bolt-on (3.1%-points). The second largest difference was seen for vitality, showing an improvement of 2.9%-points among four RD patient groups (Fabry disease, Hepatolenticular degeneration, Langerhans cell histiocytosis, and Niemann-Pick disease). However, the sleep, independence, or bone fracture bolt-ons did not improve the explanatory power.

Convergent and divergent validity of bolt-on items

Most anticipated correlations between bolt-ons and items or composite scores of the EQ-5D-5L or other instruments have been confirmed (Table 4). The dignity bolt-on showed strong correlation with the EQ-5D-5L AD dimension and SF-12 MCS in 19 and 25 RDs, respectively. Among the five core EQ-5D-5L items, four bolt-ons showed strong correlations with both MO and SC: muscle problems, oral expression, independence and dexterity (range of rs=0.53-0.77). In addition, weight control also strongly correlated with SC (rs=0.63). Five bolt-ons had strong correlations with UA: independence, bone fracture, oral expression, muscle problems and dexterity (range of rs=0.50-0.80). Fatigue, itching and sleep demonstrated strong correlations

with PD (range of rs=0.51-0.54). Eight bolt-ons showed strong correlations with AD: dignity, safety, fear, happiness, self-image, vitality, fatigue and weight control (range of rs=0.51-0.62). There were only three bolt-ons that did not show strong correlation with any of the five core EQ-5D-5L items: isolation (range of |rs|=0.20-0.47), fertility (range of |rs|=0.01-0.48) and visual acuity (range of |rs|=0.17 to 0.36). The weight control bolt-on exhibited the strongest correlation with EQ VAS (|rs|=0.55), while visual acuity the weakest (|rs|=0.21).

Psychosocial health-related bolt-on items demonstrated strong correlation with SF-12 MCS, including dignity, fear, happiness and safety (range of |rs|=0.54-0.63). Physical health-related bolt-ons, such as muscle problems and dexterity (range of |rs|=0.64-0.70) had strong correlations with SF-12 PCS. Similarly, the social relationships, isolation and self-image bolt-ons exhibited the moderate correlations with social support as measured by MOS-SSS (range of |rs|=0.30-0.34).

Known-group validity of bolt-on items

Both the EQ-5D-5L alone and the EQ-5D-5L with bolt-ons were effective in significantly differentiating between known groups in nearly all cases (Table 5). The EQ-5D-5L+bolt-ons showed higher effect sizes in 52% of group comparisons, while in the remaining cases, the EQ-5D-5L alone performed better. Several bolt-ons improved the known-groups validity in specific patient groups, for example, myasthenia gravis and spinal and bulbar muscular atrophy (muscle problems), neuromyelitis optica and multiple sclerosis (fatigue), Marfan syndrome (self-image)

and Pompe disease (safety), Huntington's disease (oral expression) and scleroderma (dexterity). The full results of the known-group validity test are presented in *Supplementary File 3*.

Discussion

This study is the first to develop EQ-5D-5L bolt-on items and examine their psychometric properties in a large-scale sample of patients with RDs. The study's strengths include its wide range of RDs, large sample size, numerous new bolt-ons developed and the comprehensive psychometric assessment. The EQ-5D-5L demonstrated good validity, evidenced by its low ceiling in most RDs and ability to discriminate among relevant known groups based on clinical characteristics. Strong psychometric evidence was found for several bolt-ons at the item level and in enhancing the overall performance of the EQ-5D-5L instrument. However, nearly all bolt-on items showed a lower ceiling and higher floor compared to the five EQ-5D-5L dimensions across multiple RDs. This suggests the relevance of the bolt-ons in capturing HRQoL in RD populations. The newly developed bolt-on items address the need for relevant outcome measures that account for the specific health dimensions affected by RDs. The majority of the new drugs approved annually by the US Food and Drug Administration or the European Medicines Agency target RDs or challenging conditions with limited effective therapies available.[39] The bolt-ons developed in the present study therefore provide useful additions for more accurately assessing HRQoL outcomes, which are essential for decision-makers evaluating the value of new, costly treatments.

Dignity was earlier tested as a bolt-on for the EQ-5D in pressure ulcer populations.[40] Our results confirm the broader applicability of this bolt-on. Consistently with the results of a previous hemophilia study,[30] this item demonstrated good distributional characteristics; however, it did not significantly reduce the ceiling of the EQ-5D-5L in most RDs. [30]Notably, in RDs such as spinocerebellar ataxia, Huntington's disease, amyotrophic lateral sclerosis, Pompe disease, isolated hypogonadotropic hypogonadism, and Dravet syndrome, over 90% of patients reported at least some problems with dignity. It also demonstrated good convergent validity with the SF-12 MCS. Additionally, it increased explanatory power of the five EQ-5D-5L items on the EQ VAS and improved known-group validity in 13 RDs. These findings suggest that the dignity bolt-on has distinct merits. Testing its usefulness in other chronic populations, where the EQ-5D-5L exhibits a higher ceiling, could be valuable.

Multiple bolt-on items showed strong correlations with one or more of the five EQ-5D-5L items, suggesting potential conceptual overlap, e.g., muscle problems with mobility or fear with anxiety/depression. This overlap may reduce the value of these bolt-ons if certain issues are double-reported. However, in most cases, strong correlations may indicate related constructs rather than an overlap, such as dignity and anxiety/depression, which are distinct constructs. The best divergent validity was observed for the isolation, fertility, visual acuity bolt-ons, which seem to capture completely different constructs. The usefulness of these items in various RDs was confirmed by the reduction in ceiling and known group validity tests. The isolation bolt-on seems particularly valuable in congenital adrenal hyperplasia, albinism and Niemann-Pick disease, visual acuity in albinism and Marfan syndrome, and fertility in isolated

hypogonadotropic hypogonadism and Kallmann syndrome. Notably, these constructs represent items in other generic HRQoL or wellbeing measures: vision (EQ-HWB, HUI, 15D), social isolation (AQOL) and fertility (HUI).[41–43]

The additional value of this study lies in the development and validation of bolt-on items relevant to not only RDs but also potentially other populations. These include condition-specific items, such as visual acuity for eye diseases, itching for skin conditions, muscle problems for musculoskeletal disorders, respiratory issues for pulmonary conditions, and weight control for obesity. Generic bolt-ons such as sleep, vitality, fatigue and social relationships could apply to various patient populations, the general population as well as caregivers. Some bolt-on items (e.g., independence, happiness, safety) could enhance the content of the EQ-5D-5L, which measures HRQoL, by adding wellbeing aspects. Additionally, while some of the newly developed bolt-ons measure overlapping conceptual constructs (e.g., vitality and fatigue), different RD groups selected different ones as their most relevant bolt-ons. Future research could focus on comparing the usefulness of these bolt-ons designed to measure similar constructs and exploring the possibility of harmonizing or combining them. Furthermore, while bolt-ons seem beneficial for the EQ-5D-5L even without value sets, more research is needed to identify the most suitable items for future valuation studies. This could support cost-utility analyses in RDs, for instance, as a sensitivity analysis of the reference case EQ-5D-5L.

The main limitation of this study is that all data were collected on a voluntary basis, which may have resulted in a lack of information from patients with poor health status or caregivers who

were unwilling to participate in the survey, creating selection bias. Additionally, all data were collected through a web-based survey, which could have excluded patients who are unfamiliar with or lack access to the internet. Moreover, the cross-sectional design of the study did not allow for testing responsiveness to change or test-retest reliability of the bolt-ons. Furthermore, while our sample size exceeds that of previous bolt-on studies in patient populations,[44–46] it may not fully represent the over 20 million people living with RDs in China. We acknowledge that the sample size was very small for some RD populations. However, since we primarily evaluated performance at the bolt-on level rather than the RD level, the sample size for psychometric evaluation was sufficient for each bolt-on. While our results may not be generalizable to all RD populations studied, we believe the study provides a valuable starting point for confirming the validity of these bolt-ons in clinical populations in China and beyond.[47] Another limitation is that most RDs are genetic conditions, which resulted in a relatively young study sample. While some RD patients have normal life expectancy, the large proportion of younger patients in our sample may have influenced the psychometric results on bolt-ons. Lastly, while there are numerous RDs, this paper focused on only 31. Given the significant heterogeneity in affected HRQoL dimensions, it is essential to test the developed bolt-ons for their applicability to conditions beyond those investigated in this study.

Conclusion

This study developed a set of EQ-5D-5L bolt-ons and psychometrically tested them in a cohort of over 9,000 Chinese patients with 31 types of RDs. Based on our findings, the EQ-5D-5L shows sufficient validity in most RDs, but incorporating specific bolt-ons could enhance its ability to

more comprehensively assess HRQoL in RD populations. Specific bolt-ons were identified that appear to be the most useful for each RD investigated. These findings can inform the selection of bolt-on items for future studies. Furthermore, the items developed may have potential applications beyond RD populations.

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Table 1 Respondents' background characteristics (N = 9,190)

	N	%
Sex		
Male	4,453	48.5
Female	4,737	51.6
Age (years)		
15-30	3,430	37.3
31-40	2,727	29.7
41-50	1,621	17.6
51-60	943	10.3
>=61	469	5.1
Employment		
Active	3,548	38.6
Non-active	5,642	61.4
Residential registry		
Urban	4,997	54.4
Rural	4,171	45.4
Family income after tax per year (*CNY 1 = USD 0.14*)		
CNY <5000	561	6.1
CNY 5001 ~ CNY 10,000	580	6.3
CNY 10,001~ CNY 30,000	1,819	19.8
CNY 30,001~ CNY 50,000	1,987	21.6
CNY 50,001~ CNY 100,000	2,441	26.6
CNY 100,001~ CNY 200,000	1,230	13.4
CNY 200,001~ CNY 300,000	335	3.7
CNY 300,001~ CNY 500,000	149	1.6
CNY >500,001	88	1.0
Years since diagnosis		
≤ 10	3,665	39.9
11~20	3,015	32.8
21~30	1,505	16.4
31~40	691	7.5
≥ 41	314	3.4
Number of children		
0	707	7.7
1	3,504	38.1
2	1,433	15.6
≥ 3	316	3.4
Refuse to answer	3,230	35.2
Caregiver		
Yes	2,366	25.8
No	6,824	74.3

Using assistive devices in daily life (e.g., wheelchair or ventilator)		
No	5,156	56.1
Rarely (<1 hour/day)	1,525	16.6
Sometimes (1-4 hours/day)	1,151	12.5
Often (5-8 hours/day)	654	7.1
Always	687	7.5
Missing	17	0.2
Genetic test (Received)		
Yes	2,780	30.3
No	6,410	69.8
EQ VAS (Mean, SD)	58.7	24.0

Table 2 Response distribution on EQ-5D-5L and bolt-on items

EQ-5D-5L	RDs	N (%)						Full Health	
		Level 1	Level 2	Level 3	Level 4	Level 5	Total	EQ-5D-5L (11111)	EQ-5D-5L+bolt-on (111111)
Mobility	All	4170 (45.4)	2374 (25.8)	1244 (13.5)	712 (7.7)	690 (7.5)	9,190	-	-
Self-care	All	6025 (65.6)	1630 (17.7)	692 (7.5)	319 (3.5)	524 (5.7)	9,190	-	-
Usual activities	All	4309 (46.9)	2667 (29.0)	1148 (12.5)	593 (6.4)	473 (5.2)	9,190	-	-
Pain/discomfort	All	2074 (22.6)	4213 (45.8)	1964 (21.4)	608 (6.6)	331 (3.6)	9,190	-	-
Anxiety/depression	All	1569 (17.1)	3972 (43.2)	2258 (24.6)	846 (9.2)	545 (5.9)	9,190	-	-
Bolt-on items									
Dignity	All	1912 (20.8)	2795 (30.4)	1773 (19.3)	1804 (19.6)	906 (9.9)	9,190	546(5.9)	370(4.0)
Safety	ALS, MG, PD	330 (13.4)	653 (26.5)	759 (30.8)	491 (19.9)	233 (9.4)	2,466	154(6.2)	88(3.6)
Independence	OI, HD, DS	73 (19.9)	101 (27.5)	84 (22.9)	24 (6.5)	85 (23.2)	367	11(3.0)	6(1.6)
Isolation	ALB, GD, NPD, EB	28 (7.3)	75 (19.5)	144 (37.4)	69 (17.9)	69 (17.9)	385	32(8.3)	0(0.0)
Fear	DMD, MS, FD, PWS, NOS, SCL	213 (9.6)	939 (42.4)	531 (24.0)	309 (14.0)	221 (10.0)	2,213	98(4.4)	44(2.0)
Happiness	LCH,LYM,MPS-I,HEM	122 (8.1)	572 (38.2)	299 (20.0)	408 (27.2)	97 (6.5)	1,498	51(3.4)	2(0.1)
Social relationships	HFH,HEP, SMA,TSC, IPA	339 (42.2)	245 (30.5)	153 (19.0)	46 (5.7)	21 (2.6)	804	68(8.5)	56(7.0)
Self-image	SCA,SBMA, KS,MFS,IHH, CAH	183 (12.6)	296 (20.3)	340 (23.3)	206 (14.1)	431 (29.6)	1,456	132(9.1)	60(4.1)
Bone fracture	OI	10 (10.0)	17 (17.0)	41 (41.0)	29 (29.0)	3 (3.0)	100	3(3.0)	0(0.0)

Respiratory problems	ALS,PD, IPA	95 (28.9)	102 (31.0)	60 (18.2)	51 (15.5)	21 (6.4)	329	1(0.3)	1(0.3)
Vitality	FD,HEP, LCH,NPD	69 (11.8)	166 (28.4)	147 (25.1)	132 (22.6)	71 (12.1)	585	62(10.6)	32(5.5)
Fatigue	HFH,MS, NOS	77 (7.2)	464 (43.4)	339 (31.7)	135 (12.6)	53 (5.0)	1,068	60(5.6)	25(2.3)
Muscle problem	DMD, SBMA, SMA,MG	200 (7.6)	1057 (39.9)	778 (29.4)	468 (17.7)	143 (5.4)	2,646	156(5.9)	60(2.3)
Itching	EB	13 (6.5)	53 (26.4)	61 (30.3)	56 (27.8)	18 (9.0)	201	7(3.5)	3(1.5)
Fertility	KS,LYM, IHH,CAH	181 (34.9)	52 (10.0)	60 (11.6)	59 (11.4)	166 (32.0)	518	52(10.0)	19(3.7)
Visual acuity	ALB,MFS	276 (28.3)	274 (28.1)	216 (22.1)	176 (18.0)	34 (3.5)	976	113(11.6)	49(5.0)
Dexterity of both hands and fingers	MPS-I,SCL	323 (36.3)	368 (41.4)	122 (13.7)	60 (6.7)	16 (1.8)	889	33(3.7)	27(3.0)
Sleep	SCA,TSC	110 (29.6)	168 (45.2)	59 (15.9)	28 (7.5)	7 (1.9)	372	14(3.8)	13(3.5)
Oral expression	HD,DS	36 (13.5)	69 (25.8)	81 (30.3)	50 (18.7)	31 (11.6)	267	8(3.0)	7(2.6)
Weight control	PWS	2(8.7)	3(13.0)	3(13.0)	6(26.1)	9(39.1)	23	2(8.7)	1(4.3)

ALB: Albinism; ALS: Amyotrophic lateral sclerosis; CAH: Congenital adrenal hyperplasia; DMD: Duchenne muscular dystrophy; DS: Dravet syndrome; EB: Epidermolysis bullosa; FD: Fabry disease; GD: Gaucher disease; HD: Huntington's disease; HEM: Hemophilia; HEP: Hepatolenticular degeneration; HFH: Homozygote familial hypercholesterolemia; IHH: Isolated hypogonadotropic hypogonadism; IPA: Idiopathic pulmonary artery hypertension; KS: Kallmann syndrome; LCH: Langerhans cell histiocytosis; LYM: Lymphangioleiomyomatosis; MFS: Marfan syndrome; MG: Myasthenia gravis; MPS-I: Mucopolysaccharidosis type I; MS: Multiple sclerosis; NOS: Neuromyelitis optica spectrum disorders; NPD: Niemann-Pick disease; OI: Osteogenesis imperfecta; PD: Pompe disease; PWS: Prader-Willi syndrome; SBMA: Spinal and bulbar muscular atrophy; SCA: Spinocerebellar ataxia; SCL: Scleroderma; SMA: Spinal Muscular atrophy; TSC: Tuberous sclerosis complex.

Table 3 Explanatory power (adjusted R^2) of the EQ-5D-5L and bolt-on items (EQ VAS as dependent variable)

Bolt-ons	RDs	N	EQ-5D-5L alone (%)	EQ-5D-5L + bolt-on(s) (%)	Difference in R^2 (%-point)	Rank of difference
Dignity	All	9,190	29.5	32.5	3	1
Vitality	FD,HEP,LCH,NPD	585	21.6	24.6	3	2
Self-image	SCA,SBMA,KS,MFS,IHH,CAH	1,456	27.8	30.6	2.8	3
Happiness	LCH,LYM,MPS-I,HEM	1,498	34.5	37.1	2.6	4
Fatigue	HFH,MS,NOS	1,068	30.3	32.8	2.5	5
Isolation	ALB, GD, NPD, EB	385	35.8	38.3	2.5	6
Muscle problem	DMD,SBMA,SMA,MG	2,646	30.4	32.9	2.5	7
Safety	ALS,MG,PD	2,466	31.2	33.1	1.9	8
Social relationships	HFH,HEP,SMA,TSC,IPA	804	23.2	24.4	1.2	9
Oral expression	HD,DS	267	27.8	29.0	1.2	10
Weight control	PWS	23	39.3	40.3	1	11
Fear	DMD,MS,FD,PWS,NOS, SCL	2,213	26.2	27.1	0.9	12
Respiratory problems	ALS,PD,IPA	329	24.7	25.3	0.6	13
Itching	EB	201	31.2	31.7	0.5	14
Dexterity of both hands and fingers	MPS-I,SCL	889	23.7	23.8	0.1	15
Fertility	KS,LYM,IHH,CAH	518	30.6	30.8	0.2	16

Visual acuity	ALB,MFS	976	26.8	26.9	0.1	17
Sleep	SCA,TSC	372	23.1	23.0	-0.1	18
Independence	OI,HD,DS	367	27.6	27.4	-0.2	19
Bone fracture	OI	100	14.1	13.8	-0.3	20

ALB: Albinism; ALS: Amyotrophic lateral sclerosis; CAH: Congenital adrenal hyperplasia; DMD: Duchenne muscular dystrophy; DS: Dravet syndrome; EB: Epidermolysis bullosa; FD: Fabry disease; GD: Gaucher disease; HD: Huntington's disease; HEM: Hemophilia; HEP: Hepatolenticular degeneration; HFH: Homozygote familial hypercholesterolemia; IHH: Isolated hypogonadotropic hypogonadism; IPA: Idiopathic pulmonary artery hypertension; KS: Kallmann syndrome; LCH: Langerhans cell histiocytosis; LYM: Lymphangioleiomyomatosis; MFS: Marfan syndrome; MG: Myasthenia gravis; MPS-I: Mucopolysaccharidosis type I; MS: Multiple sclerosis; NOS: Neuromyelitis optica spectrum disorders; NPD: Niemann-Pick disease; OI: Osteogenesis imperfecta; PD: Pompe disease; PWS: Prader-Willi syndrome; SBMA: Spinal and bulbar muscular atrophy; SCA: Spinocerebellar ataxia; SCL: Scleroderma; SMA: Spinal Muscular atrophy; TSC: Tuberous sclerosis complex.

Table 4 Convergent and divergent validity of the bolt-on items

Bolt-ons	RDs	N	SF-12 MCS	EQ-5D-5L AD	SF-12 PCS	EQ-5D-5L MO	EQ-5D-5L SC	EQ-5D-5L UA	EQ-5D-5L PD	EQ VAS	Social Support
Dignity	ALB	117	-0.58	0.50	-0.57	0.33	0.24	0.35	0.17	-0.43	-0.43
	OI	100	-0.55	0.49	-0.34	0.26	0.22	0.37	0.37	-0.30	-0.31
	HFH	18	-0.38	0.55	-0.37	0.29	0.00	0.25	0.39	-0.40	-0.04
	DMD	113	-0.63	0.53	0.04	-0.04	-0.04	0.05	0.17	-0.31	-0.31
	MS	731	-0.54	0.47	-0.41	0.38	0.35	0.41	0.31	-0.46	-0.34
	FD	173	-0.59	0.53	-0.36	0.26	0.12	0.22	0.23	-0.27	-0.16
	HEP	354	-0.59	0.57	-0.45	0.34	0.37	0.39	0.46	-0.38	-0.40
	GD	58	-0.63	0.58	-0.46	0.46	0.26	0.43	0.34	-0.62	-0.21
	HD	263	-0.54	0.57	-0.48	0.51	0.46	0.50	0.49	-0.44	-0.13
	ALS	196	-0.50	0.60	-0.27	0.33	0.39	0.43	0.45	-0.37	-0.05
	SCA	181	-0.46	0.47	-0.36	0.34	0.28	0.31	0.24	-0.43	-0.24
	SBMA	155	-0.59	0.48	-0.15	0.22	0.10	0.16	0.34	-0.35	-0.34
	SMA	214	-0.58	0.56	-0.41	0.44	0.43	0.38	0.43	-0.43	-0.38
	TSC	191	-0.48	0.48	-0.38	0.22	0.30	0.38	0.36	-0.43	-0.25
	KS	141	-0.54	0.51	-0.34	0.08	-0.06	-0.11	0.24	-0.35	-0.25
	LCH	49	-0.62	0.56	-0.43	0.21	0.24	0.48	0.59	-0.48	-0.48
	LYM	256	-0.60	0.48	-0.44	0.39	0.36	0.41	0.38	-0.50	-0.21
	MFS	859	-0.53	0.57	-0.45	0.36	0.20	0.38	0.39	-0.45	-0.34
	MPS-I	35	-0.71	0.48	-0.04	0.19	0.18	0.18	0.18	-0.53	-0.53
	PWS	23	-0.49	0.53	-0.60	0.55	0.52	0.34	0.62	-0.53	-0.36
	MG	2164	-0.56	0.54	-0.44	0.42	0.40	0.42	0.37	-0.44	-0.32
	NOS	319	-0.55	0.55	-0.52	0.49	0.43	0.49	0.43	-0.40	-0.42
	PD	106	-0.70	0.56	-0.25	0.45	0.39	0.44	0.40	-0.40	-0.40
	IHH	88	-0.54	0.67	-0.17	0.18	0.16	0.17	0.17	-0.50	-0.51
	IPA	27	-0.70	0.28	-0.33	0.41	0.32	0.35	0.28	-0.16	-0.32
	SCL	854	-0.54	0.47	-0.38	0.32	0.27	0.29	0.29	-0.40	-0.24
	CAH	33	-0.43	0.47	-0.02	-0.14	-0.14	-0.14	0.09	-0.42	-0.24
	HEM	1158	-0.60	0.57	-0.37	0.39	0.30	0.40	0.33	-0.42	-0.32

	EB	201	-0.63	0.61	-0.34	0.22	0.24	0.26	0.34	-0.39	-0.39
	Total	9190	-0.57	0.55	-0.43	0.39	0.36	0.41	0.37	-0.44	-0.31
Safety	ALS	196	-0.58	0.55	-0.24	0.28	0.33	0.39	0.45	-0.37	-0.05
	MG	2164	-0.59	0.56	-0.41	0.39	0.38	0.41	0.36	-0.41	-0.36
	PD	106	-0.71	0.63	-0.28	0.46	0.39	0.44	0.40	-0.37	-0.24
	Total	2466	-0.61	0.57	-0.43	0.42	0.39	0.43	0.39	-0.43	-0.33
Independence	OI	100	-0.03	0.13	-0.44	0.44	0.37	0.46	0.23	-0.02	-0.03
	HD	263	-0.42	0.49	-0.62	0.73	0.72	0.74	0.42	-0.41	-0.03
	Total	367	-0.40	0.45	-0.59	0.64	0.68	0.69	0.38	-0.35	-0.02
Isolation	ALB	117	-0.56	0.43	-0.46	0.38	0.24	0.41	0.20	-0.38	-0.35
	GD	58	-0.52	0.44	-0.43	0.32	0.26	0.29	0.30	-0.47	-0.19
	EB	201	-0.49	0.47	-0.45	0.33	0.33	0.41	0.45	-0.45	-0.38
	Total	385	-0.50	0.45	-0.45	0.34	0.30	0.39	0.33	-0.44	-0.33
Fear	DMD	113	-0.56	0.64	0.09	-0.06	0.07	0.00	0.28	-0.25	0.16
	MS	731	-0.51	0.64	-0.30	0.21	0.24	0.26	0.36	-0.36	-0.25
	FD	173	-0.57	0.62	-0.31	0.26	0.16	0.30	0.28	-0.19	-0.19
	PWS	23	-0.08	0.12	-0.45	0.20	0.04	0.11	0.12	-0.03	-0.05
	NOS	319	-0.55	0.62	-0.37	0.32	0.33	0.34	0.33	-0.33	-0.43
	SCL	854	-0.57	0.62	-0.27	0.24	0.24	0.25	0.32	-0.33	-0.21
	Total	2213	-0.54	0.62	-0.30	0.23	0.22	0.26	0.34	-0.33	-0.25
Happiness	LCH	49	-0.67	0.53	-0.35	0.19	0.22	0.30	0.34	-0.43	-0.53
	LYM	256	-0.71	0.56	-0.37	0.33	0.33	0.35	0.38	-0.50	-0.27
	MPS-I	35	-0.66	0.71	-0.33	0.53	0.40	0.46	0.48	-0.54	0.17
	HEM	1158	-0.61	0.51	-0.28	0.34	0.26	0.33	0.30	-0.39	-0.34
	Total	1498	-0.63	0.53	-0.33	0.36	0.29	0.35	0.35	-0.43	-0.34
Social relationships	HFH	18	-0.37	0.51	-0.15	0.35	0.34	0.33	0.43	-0.33	-0.05
	HEP	354	-0.48	0.37	-0.30	0.22	0.20	0.23	0.34	-0.22	-0.40
	SMA	214	-0.40	0.38	-0.19	0.27	0.30	0.23	0.23	-0.24	-0.30
	TSC	191	-0.45	0.31	-0.44	0.20	0.30	0.39	0.38	-0.39	-0.27
	IPA	27	-0.32	0.08	-0.31	0.44	0.27	0.40	0.48	-0.19	-0.31
	Total	804	-0.45	0.35	-0.18	0.09	0.20	0.16	0.31	-0.24	-0.34
	SCA	181	-0.44	0.47	-0.33	0.27	0.26	0.27	0.32	-0.38	-0.31

Self-image	SBMA	155	-0.54	0.47	-0.19	0.16	0.07	0.22	0.35	-0.33	-0.27
	KS	141	-0.55	0.51	-0.39	0.10	-0.08	-0.05	0.31	-0.48	-0.27
	MFS	858	-0.49	0.50	-0.44	0.30	0.18	0.32	0.33	-0.39	-0.28
	IHH	88	-0.54	0.53	-0.08	0.20	0.22	0.13	0.19	-0.38	-0.40
	CAH	33	-0.35	0.48	0.02	0.26	0.26	0.26	0.13	-0.30	-0.37
	Total	1456	-0.50	0.51	-0.37	0.28	0.19	0.29	0.32	-0.40	-0.30
Oral expression	HD	263	-0.38	0.47	-0.69	0.77	0.75	0.80	0.48	-0.48	-0.06
	Total	267	-0.39	0.47	-0.69	0.77	0.75	0.80	0.48	-0.48	-0.05
Sleep	SCA	181	-0.42	0.53	-0.28	0.36	0.39	0.33	0.55	-0.27	0.10
	TSC	191	-0.42	0.41	-0.40	0.33	0.23	0.36	0.46	-0.31	-0.15
	Total	372	-0.43	0.48	-0.32	0.31	0.31	0.33	0.51	-0.29	-0.02
Bone fracture	OI	100	0.05	-0.04	-0.45	0.45	0.34	0.50	0.20	0.03	0.00
Respiratory problem	ALS	196	-0.38	0.49	-0.33	0.44	0.40	0.52	0.52	-0.37	0.03
	PD	106	-0.44	0.46	-0.58	0.65	0.65	0.64	0.58	-0.52	-0.10
	IPA	27	-0.74	0.47	-0.64	0.55	0.37	0.51	0.42	-0.21	-0.01
	Total	329	-0.37	0.42	-0.43	0.43	0.32	0.46	0.49	-0.38	-0.03
Vitality	FD	173	-0.63	0.55	-0.53	0.40	0.24	0.38	0.38	-0.35	-0.33
	HEP	354	-0.62	0.62	-0.52	0.39	0.37	0.41	0.48	-0.41	-0.31
	LCH	49	-0.64	0.53	-0.51	0.18	0.38	0.28	0.28	-0.48	-0.32
	Total	585	-0.62	0.60	-0.55	0.39	0.32	0.41	0.47	-0.41	-0.32
Fatigue	HFH	18	-0.39	0.58	-0.38	0.76	0.43	0.62	0.50	0.09	0.04
	MS	731	-0.57	0.51	-0.53	0.41	0.42	0.44	0.49	-0.50	-0.22
	NOS	319	-0.56	0.59	-0.51	0.53	0.49	0.49	0.54	-0.43	-0.30
	Total	1068	-0.57	0.54	-0.52	0.45	0.44	0.46	0.51	-0.48	-0.24
Muscle problem	DMD	113	-0.22	0.17	-0.40	0.72	0.71	0.76	0.39	-0.34	-0.20
	SBMA	155	-0.13	0.20	-0.41	0.61	0.53	0.64	0.31	-0.40	-0.04
	SMA	214	-0.43	0.35	-0.57	0.63	0.53	0.54	0.33	-0.35	-0.16
	MG	2164	-0.46	0.41	-0.64	0.60	0.55	0.60	0.47	-0.46	-0.16
	Total	2646	-0.36	0.38	-0.70	0.70	0.63	0.70	0.43	-0.49	-0.17
Itching	EB	201	-0.41	0.47	-0.37	0.28	0.37	0.34	0.54	-0.39	-0.21
Fertility	KS	141	-0.30	0.34	0.22	-0.06	0.17	-0.08	-0.01	-0.18	-0.18
	LYM	256	-0.12	0.22	0.01	-0.04	-0.02	0.01	0.17	-0.01	-0.12

	IHH	88	-0.30	0.48	-0.03	0.07	0.13	0.11	0.10	-0.20	-0.36
	CAH	33	-0.16	0.22	-0.25	-0.21	-0.21	-0.21	0.14	-0.30	0.12
	Total	518	-0.21	0.34	0.29	0.36	0.22	0.31	0.17	-0.05	-0.21
Visual acuity	ALB	117	-0.41	0.29	-0.41	0.36	0.20	0.28	0.31	-0.31	-0.14
	MFS	859	-0.26	0.23	-0.32	0.36	0.20	0.37	0.24	-0.24	-0.10
	Total	976	-0.24	0.21	-0.24	0.34	0.18	0.36	0.17	-0.21	-0.11
Dexterity of both hands and fingers	MPS-I	35	-0.36	0.33	-0.36	0.42	0.68	0.57	0.39	-0.50	-0.09
	SCL	854	-0.27	0.22	-0.63	0.52	0.51	0.58	0.48	-0.29	-0.07
	Total	889	-0.26	0.22	-0.64	0.53	0.54	0.59	0.48	-0.31	-0.06
Weight control	PWS	23	-0.18	0.56	-0.36	0.22	0.63	0.15	0.40	-0.55	-0.17

Note: Based on Spearman's correlation analysis, light grey: $p<0.05$, grey: $p<0.01$, and dark grey: $p<0.001$

ALB: Albinism; ALS: Amyotrophic lateral sclerosis; CAH: Congenital adrenal hyperplasia; DMD: Duchenne muscular dystrophy; DS: Dravet syndrome; EB: Epidermolysis bullosa; FD: Fabry disease; GD: Gaucher disease; HD: Huntington's disease; HEM: Hemophilia; HEP: Hepatolenticular degeneration; HFH: Homozygote familial hypercholesterolemia; IHH: Isolated hypogonadotropic hypogonadism; IPA: Idiopathic pulmonary artery hypertension; KS: Kallmann syndrome; LCH: Langerhans cell histiocytosis; LYM: Lymphangioleiomyomatosis; MFS: Marfan syndrome; MG: Myasthenia gravis; MPS-I: Mucopolysaccharidosis type I; MS: Multiple sclerosis; NOS: Neuromyelitis optica spectrum disorders; NPD: Niemann-Pick disease; OI: Osteogenesis imperfecta; PD: Pompe disease; PWS: Prader-Willi syndrome; SBMA: Spinal and bulbar muscular atrophy; SCA: Spinocerebellar ataxia; SCL: Scleroderma; SMA: Spinal Muscular atrophy; TSC: Tuberous sclerosis complex.

Correlation coefficients for patients with DS (n=4) and NPD (n=9) were not calculated for bolt-on items separately, given the sample sizes are too small. However, they were included in the overall sample for the estimation of correlation coefficients for each bolt-on item.

Table 5 Known-group validity of EQ-5D-5L (+bolt-on items).

Bolt-ons	RDs	Number of significant differentiations #		Effect size (Cohen's D)	
		a. EQ-5D-5L LSSs	b. EQ-5D-5L+ bolt-on LSSs	b>a	b<a
Dignity	ALB	3	2	2	0
	ALS	1	1	0	1
	EB	3	3	2	1
	FD	3	3	1	2
	GD	1	1	0	1
	HD	10	10	8	2
	HEM	4	4	2	2
	HEP	9	10	8	2
	HFH	1	1	1	0
	IHH	2	3	3	0
	KS	1	2	1	1
	MFS	10	10	8	2
	MG	8	8	4	4
	MPS-I	1	1	0	1
	MS	10	10	7	3
	NOS	7	8	4	4
	NPD	1	1	1	0
	OI	1	1	0	1
	PD	3	3	0	3
	PWS	4	5	4	1
	SBMA	7	7	0	7
	SCA	9	9	3	6
	SCL	10	10	2	8
	SMA	5	5	4	1
	TSC	2	3	3	0
Safety	ALS	1	1	1	0
	MG	8	7	2	5
	PD	3	3	3	0
Independence	HD	10	10	4	6
	OI	1	1	0	1
Isolation	ALB	3	1	0	1
	EB	3	3	0	3
	GD	3	3	0	3
	NPD	1	1	1	0
Fear	FD	3	3	1	2
	MS	10	10	4	6
	NOS	7	8	1	7
	PWS	4	5	1	4

	SCL	10	10	1	9
Happiness	HEM	4	4	2	2
	MPS-I	1	1	1	0
Social relationships	HEP	9	10	4	6
	HFH	1	1	0	1
	SMA	5	5	1	4
	TSC	2	3	3	0
Self-image	IHH	2	3	3	0
	KS	1	1	0	1
	MFS	10	10	7	3
	SBMA	7	7	0	7
	SCA	9	9	3	6
Bone fracture	OI	1	1	0	1
Respiratory problems	ALS	1	1	0	1
	PD	3	3	2	1
Vitality	FD	3	3	1	2
	HEP	9	10	1	9
	NPD	1	1	1	0
Fatigue	HFH	1	2	2	0
	MS	10	10	7	3
	NOS	7	7	7	0
Muscle problems	SBMA	7	8	8	0
	SMA	5	5	3	2
	MG	8	8	8	0
Itchiness	EB	3	3	2	1
Fertility	IHH	2	3	2	1
	KS	3	3	2	1
Visual acuity	ALB	3	1	1	0
	MFS	10	10	6	4
Dexterity of both hands/fingers	MPS-I	1	1	0	1
	SCL	10	10	10	0
Sleep	SCA	9	9	5	4
	TSC	2	3	1	2
Oral expression	HD	10	10	10	0
Weight control	PWS	4	5	3	2

The bolt-on items statistically and significantly distinguish between patients with specific symptoms, clinical conditions, or side effects from those without.

ALB: Albinism; ALS: Amyotrophic lateral sclerosis; CAH: Congenital adrenal hyperplasia; DMD: Duchenne muscular dystrophy; DS: Dravet syndrome; EB: Epidermolysis bullosa; FD: Fabry disease; GD: Gaucher disease; HD: Huntington's disease; HEM: Hemophilia; HEP: Hepatolenticular degeneration; HFH: Homozygote familial hypercholesterolemia; IHH: Isolated hypogonadotropic hypogonadism; IPA: Idiopathic pulmonary artery hypertension; KS: Kallmann syndrome; LCH: Langerhans cell histiocytosis; LYM: Lymphangioleiomyomatosis; MFS: Marfan syndrome; MG: Myasthenia gravis; MPS-I: Mucopolysaccharidosis type I; MS: Multiple sclerosis; NOS: Neuromyelitis optica spectrum disorders; NPD: Niemann-Pick disease; OI: Osteogenesis imperfecta; PD: Pompe disease; PWS: Prader-Willi syndrome; SBMA: Spinal and bulbar muscular atrophy; SCA: Spinocerebellar ataxia; SCL: Scleroderma; SMA: Spinal Muscular atrophy; TSC: Tuberous sclerosis complex.

Figure 1 Sample size for each RD