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Effectiveness of generic Quality of Life (QoL) questionnaires in Spinal Muscular Atrophy (SMA) and Duchenne Muscular Dystrophy (DMD)

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BACKGROUND

- **Current Policy:** Many countries require cost effectiveness studies for approval and reimbursement of drugs, quantifying health benefits for treatments using quality-adjusted life years (QALY's) based on the EuroQoL 5 questionnaire (EQ-5D-5L). Considering the high costs of treatments for rare diseases, it is of importance to accurately capture their treatment effect on patients. However, the EQ-5D-5L might not capture all relevant health benefits of these diseases.
- Therefore, this research analyzes the extent to which current general pediatric and adult questionnaires used for QALYs measurement capture the patient-perceived health-related utility (HRQoL) values of treatments for rare diseases, particularly Spinal Muscular Atrophy (SMA) and Duchenne Muscular Dystrophy (DMD).

Box 1: SMA and DMD

Spinal Muscular Atrophy (SMA)

- A rare genetic and neuromuscular disorder characterized by proximal muscular weakness and atrophy. It affects the quality of life severely, with currently being the most common genetic cause of infant mortality due to respiratory failure.

Duchenne Muscular Dystrophy (DMD)

- A rare genetic and neuromuscular disorder causing weakening and atrophy of muscles which manifests before the age of six. It mainly affects boys. The quality of life is severely affected as the disease causes long-term disability.

OBJECTIVE

- To evaluate the effectiveness of commonly used quality-of-life (QoL) questionnaires for SMA and DMD in capturing HRQoL values, with a particular focus on EQ-5D-5L.
- To quantify the extent to which these instruments reflect the individual patient-perceived health-related utility values associated SMA and DMD with treatments.

METHODS

- Firstly, a literature review was conducted to identify the key domains (broader categories) and themes (subcategories) relevant to SMA and DMD as well as the most commonly used QoL questionnaires and their dimensions and levels.
- Secondly, the content validity of five prevalent QoL instruments — EQ-5D-5L, SF-36, PROMIS-29, and PedsQL 4.0 GCS NMM and DMM— was systematically evaluated against these identified domains and themes.
- Lastly, Expert interviews were conducted to enrich the understanding of the applicability of generic questionnaires in rare diseases and to explore alternative HRQoL measurement methods.

Box 2: HRQoL Questionnaires

A literature review was conducted to assess the most frequently used HRQoL questionnaires to capture patient-perceived health-related utility values in patients with SMA and DMD. The EQ-5D-5L, SF-36, and PROMIS-29 emerged as general HRQoL questionnaires for adults, assessing various health dimensions. Additionally, the PedsQL 4.0 Generic Core Scales (GCS), Neuromuscular Module (NMM), and Duchenne Muscular Dystrophy Module (DMM) are pediatric, disease-specific tools (DMS) for neuromuscular and muscular dystrophy conditions.

- **EQ-5D-5L:** A standardized measure of HRQoL developed by the EuroQol Group, covering 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain consists of 5 levels.
- **SF-36:** A 36-item survey measuring physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.
- **PROMIS-29:** Assesses physical function, pain interference, fatigue, sleep disturbance, depressive symptoms, anxiety, and social roles.
- **PedsQL 4.0 GCS, NMM, and DMM:** Measures physical, emotional, social, and school functioning in children. Specifically designed for pediatric patients with neuromuscular and muscular dystrophy, including SMA and DMD.

RESULTS

- Five main domains and their underlying themes were identified: physical; social; physiological; well-being; and the "other" domain, which contained accessibility/wheelchair use, healthcare service provision and treatment related effects.
- EQ-5D-5L appeared to be insufficient in covering relevant themes for SMA and DMD, with only 35% of the psychological domain, 40% of the physical domain, and nothing of the social domain adequately addressed. SF-36 and PROMIS-29 provided more extensive coverage, yet still lacked critical aspects on the "other" domain.
- PedsQL modules measured HRQoL most accurately, but not fully.

Table 1. Identified SMA and DMD Domains and their Underlying Themes[1]

Physical Domain	Well-being Domain	Psychological Domain	Social Domain	Other Domain
General physical QoL	General well-being	General psychosocial quality of life	Social quality of life	Accessibility / Wheelchair use
Health behaviour	Independence / self-care	Happiness	Participation	Healthcare service provision
Sleep	Dignity	Depression	Friends	Family resources
Pain	Energy / Fatigue	Anxiety	Relationships	Carer Burden
Activities of a daily living		Coping	School / Work	Treatment and Therapy Effects

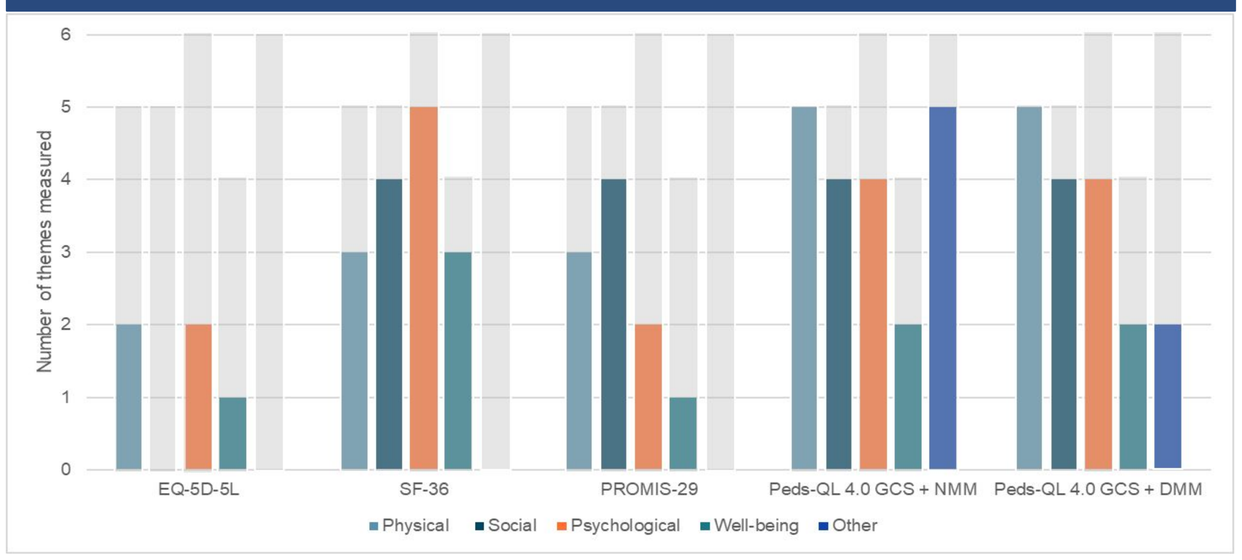
Expert Opinion on EQ-5D-5L:

- All Experts agreed upon EQ-5D-5L's benefits, such as its ability to ensure comparability of utility values across diseases. In addition, they also acknowledge the questionnaire's measurement limitations compared to disease-specific questionnaires. This makes the EQ-5D-5L in certain aspects, such as the need for mapping, a second-best solution when compared to directly using instruments tailored to specific conditions.
- However, there were also conflicting opinions between Experts on the EQ-5D-5L.
  - Expert A (member of EuroQol group) defends the EQ-5D-5L, noting it is meant to capture broad disease differences, not small, specific ones. The expert argues that if the 5 dimensions and levels do not reflect differences in rare diseases, those differences are likely minimal. While disease-specific questionnaires may measure utilities better, Expert A believes these differences may be too small to significantly impact ICER values. It would be of interest to conduct further research into this topic.
  - Expert B (expert in quality of life measurement of rare diseases) argues that EQ-5D-5L's limitations are not specific to rare diseases and that EQ-5D-5L therefore performs poorly across different disease areas. Therefore, EQ-5D-5L's limitations are applicable to both rare and more common diseases, defending its worldwide usage and validation.

Expert Opinion on Alternative Methods:

- The Experts unanimously agree on the need to enhance the specificity and sensitivity of the EQ-5D-5L by developing Bolt-ons. Additionally, if decision bodies require greater sensitivity in HRQoL measurements, Experts recommend using disease-specific questionnaires and involving patients in the development process.
- Alternative methods could be employed such as the use of Value Flower; the use of Multi-Criteria Decision Analysis (MCDA); and reporting two separate ICERs—one using EQ-5D-5L and another using a more tailored questionnaire or Value Flower. This provides decision-makers with a more comprehensive view. However, future research is needed in these areas before these methods can be employed.

Figure 1. Overlapping and missing themes in the EQ-5D-5L; SF-36; PROMIS-29; PedsQL 4.0 GCS and 3.0 NMM; the PedsQL 4.0 GCS and 3.0 DMM, for SMA and DMD



DISCUSSION

- Despite the broad recognition of the benefits that general questionnaires can bring in measuring HRQoL, the methods employed have often been criticized for their limitations in capturing the full spectrum of patient experiences, particularly considering rare diseases. This inadequacy means that these questionnaires may not fully reflect the true utility values of treatments for these conditions.
- Our analysis demonstrated that all 5 questionnaires fall short in adequately capturing all relevant identified domains and their themes of HRQoL for SMA and DMD.
  - Compared to the EQ-5D, the SF-36 is more encompassing of all domains. The themes of general well-being, coping and happiness are only captured by the SF-36, compared to all other generic questionnaires. Yet, it is not a comprehensive tool either.
  - For disease-specific questionnaires, both of the PedsQL modules cover the themes the best. The physical domain is fully captured by both the modules, which could be explained as the posed questions are tailored specifically to patients with SMA and DMD.
- Based on these findings, although these questionnaires do not fully capture all identified themes, we can conclude that the PedsQL 4.0 GCS NMM and DMM modules capture relevant disease themes most comprehensively for children with the diseases, and the SF-36 questionnaire for adults. PROMIS-29 and EQ-5D both appear to lack substantial coverage.

CONCLUSION

This analysis indicates that generic QoL questionnaires, including EQ-5D, are insufficient for capturing the complete health-related utility values for SMA and DMD. These findings advocate for enhancing the dimensions for the EQ-5D (Bolt-ons) or using disease-specific measures as additional measurement instruments to the EQ-5D.

Box 2: Policy Implications and Recommendations

- There is a need for reconsideration of the standard measurement for assessing HRQoL values for the rare diseases.
- While the exclusive use of EQ-5D-5L is not recommended, it is suggested to develop Bolt-ons tailored to SMA and DMD.
- The valuation of health states should involve input from both the general public and patients to capture diverse perspectives.
- Exploring the use of two separate ICER's are encouraged. One ICER would utilize utility values from EQ-5D-5L, the other would utilize utility values guided by the qualitative use of the Value Flower.
- The use of the MCDA method requires extensive further research before it can be employed.

DISCLOSURES

This project was conducted as part of an internship at Roche Norge A/S.

REFERENCES

[1]Uttley, L., Carlton, J., Woods, H. B., & Brazier, J. (2018). A review of quality of life themes in Duchenne muscular dystrophy for patients and carers. *Health and Quality of Life Outcomes*, *16*(1). https://doi.org/10.1186/s12955-018-1062-0