POSC30

Associations between physical function measures and patient-reported outcomes in Pompe disease and other rare disorders impacting motor, respiratory and skeletal function

Shohet S[1], Keyzor I[1], Kopiec A[2], Zalewska M[2], Brougham M[3]

[1]Amicus Therapeutics UK LTD., Marlow, BKM, UK; [2]Certara Evidence and Access, Crakow, Poland; [3]Certara Evidence and Access, Montreal, Canada

BACKGROUND

- In multisystemic rare disease studies and clinical trials, a wide range of functional and physical measures are deployed, often alongside patient-reported outcome (PRO) and quality of life (QoL) instruments.
- Investigation of the associations between these physician-assessed physical function outcomes and PROs are complex and are often not systematically explored.
- We wanted to understand if there is any evidence of these associations in the current literature.

OBJECTIVE

- To assess how motor, respiratory and skeletal function in rare disorders are associated with PROs.

METHODS

- Electronic literature searches of the MEDLINE database via PubMed were performed on 30 November 2020 for the following rare disorders: Pompe disease (PD), Morquio syndrome (MQS), hypophosphatasia (HP), X-linked hypophosphataemia (HPT), spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), and fibrodysplasia ossificans progressiva (FOP).
- Medical Subject Headings (MeSH) terms and non-MeSH words were used for the literature search. These terms were categorised into groups: 'population', 'outcomes' and 'correlation', adjusting for syntax, descriptors and adequacy of applying additional filters according to the database. The study selection process, consistent with PRISMA guidelines, involved two steps (**Figure 1**):
  - First, all titles and abstracts from the search results were screened against the inclusion criteria to identify potentially relevant papers (**Table 1**)
  - Second, full-text publications of the eligible studies were obtained and examined for inclusion in the review.

Figure 1. Flowchart of selection process (date of the searches: 30 November 2020)

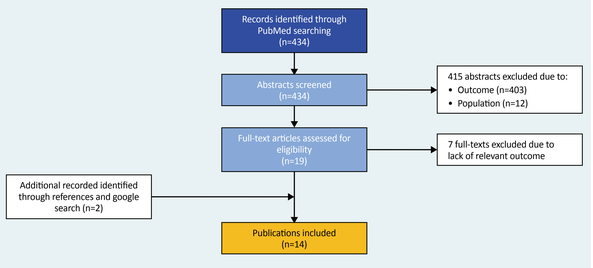


Table 1. Eligibility criteria

Category	Inclusion criteria	Exclusion criteria
Population	Pompe disease Morquio syndrome Hypophosphatasia X-linked hypophosphataemia Spinal muscular atrophy Duchenne muscular dystrophy Fibrodysplasia ossificans progressive	Healthy subjects Animal studies
Intervention	NR	NR
Outcomes	Physician-assessed functional measures Patient-reported quality of life	Beyond the scope
Study design	NR	NR
Language	English language	Non-English language

NR, not restricted.

RESULTS

- Of 434 records from PubMed, 14 eligible studies examined physical function, PROs, and QoL in four disease areas: PD, SMA, MQS and DMD (**Table 2**).

Table 2. Selected clinical studies included in literature review[1–14]

Study	n	Disease	Physical function instrument used	PRO instruments used
Binz C *et al* 2021	18	SMA	HFMSE, RULM	EQ-5D-5L
Lampe C *et al* 2015	24	MQS	Physical fatigue	EQ-5D-5L
Berger KI *et al* 2019	276	PD	3MSCT, 6MWT, FVC, MVV	SF-36
Boentert M *et al* 2015	65	PD	FVC	SF-36
Yuan M *et al* 2020	121	PD	FVC	SF-36
Gocheva V *et al* 2019	34	DMD	6MWT, FVC, MMT, HHD	PedsQL
de Moura MC *et al* 2015	34	DMD	MFM	AUQEI, WHOQOL
McDonald CM *et al* 2010	52	DMD	MFM	PedsQL, PODCI
Houwen-van Opstal SL *et al* 2014	40	DMD	10MTWR, Vignos, walking velocity	KIDSCREEN-52
Kohler M *et al* 2005	35	DMD	A6MCT, Brooke, MFM, Vignos	SF-36
Messina S *et al* 2016	98	DMD	FVC, disability summary score	PedsQL
Henricson E *et al* 2013	24/13*	DMD	10MTWR, 6MWT, NSAA, Gowers	PedsQL, PODCI
Bray P *et al* 2010	35	DMD	6MWD, 10MTRW	PedsQL
Elsenbruch S *et al* 2013	11/15/24†	DMD	Vignos	SF-36, DISABKIDS

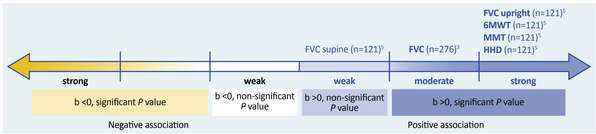
*A total of 24 patients were assessed at baseline, and 13 patients were assessed at 1-year follow-up; †n=15 children aged 8 to 12 years; n=11 adolescents aged 13–16 years; n=24 young adults aged 17–23 years. 3MSCT, 3-minute stair/climb test; 6MWT, 6-minute walk test; 10MTWR, 10-metre timed walk/run; A6MCT, assisted 6-minute cycling test; AUQEI, Autoquestionnaire Qualité de Vie Enfant Imagé; FVC, forced vital capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; HHD, hand-held dynamometry; NSAA, North Star Ambulatory Assessment; MFM, Motor Function Measure; MMT, manual muscle testing; MVV, maximum voluntary velocity; RULM, Revised Upper Limb Module; SF-36, 36-item Short Form questionnaire; WHOQOL, World Health Organization Quality of Life instruments.

- In line with other rare disease studies, the patient population size in the selected studies was relatively small, ranging from n=11 (Elsenbruch *et al* 2013) to n=276 (Berger *et al* 2019; **Table 2**).
- A broad spectrum of functional measures was used across the studies to assess patients' physical function (**Table 2**):
  - The most common functional measures used across the studies were the 6-minute walk test (6MWT) and the forced vital capacity (FVC) assessment.
- A total of eight PRO instruments were used differentially across the studies (**Table 2**):
  - The 36-item short-form instrument (SF-36) was frequently used in PD and DMD studies
  - The EUROQOL-5 dimension-5 level instrument (EQ-5D-5L) was used in SMA and MQS studies
  - Other identified PRO instruments including the Pediatric Quality of Life inventory (PedsQL) and the Pediatric Outcomes Data Collection Instrument (PODCI) were exclusively used across the nine DMD studies.
- Of the nine DMD studies, 44 correlations were reported (n range = 11–98), while one MQS study reported 24 correlations (n=24). A total of 3 PD studies reported 15 correlations (n range = 65–276), and one SMA study reported 2 correlations between functional and PRO measures (n=18).

Study summaries

- Using a mixed-effects linear regression, Berger and colleagues found a moderate positive correlation between the SF-36–Physical Component Summary (PCS) scores and FVC in patients with late-onset PD[3] (**Figure 2**)
  - A 10% increase in FVC was associated with improvements of >1% in the SF-36–PCS score.

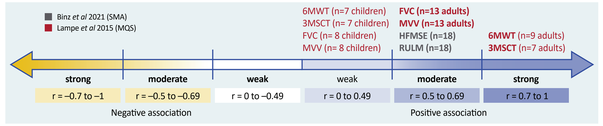
Figure 2. Correlations between functional measures and SF-36–PCS in PD



Reported associations are based on regression coefficients. **Bold** indicates a statistically significant indication.

- Also in late-onset PD, Yuan *et al* 2020 (**Figure 2**) found a strong correlation between SF-36–PCS and 6MWT, upright FVC, MMT and HHD[5]
  - A 1% increase in predicted 6MWT was associated with a 0.25-unit gain in SF-36–PCS scores.[5]
- In SMA, Binz *et al* 2021 reported moderate and significant correlations between the EQ-5D-5L visual analogue scale and the HFMSE and RULM scores[1] (**Figure 3**).
- In MQS, Lampe *et al* 2015 reported a strong and statistically significant correlation between EQ-5D-5L utility score and the two endurance parameters, 6MWT (R=0.713; *P*=0.0019) and 3MSCT (R=0.693; *P*=0.0060)[2] (**Figure 3**)
  - An increase of 100 metres in the 6MWT distance was associated with a 0.2 increase in the EQ-5D-5L utility score. This is consistent with the highest correlation found between the 6MWT and EQ-5D-5L scores.[2]

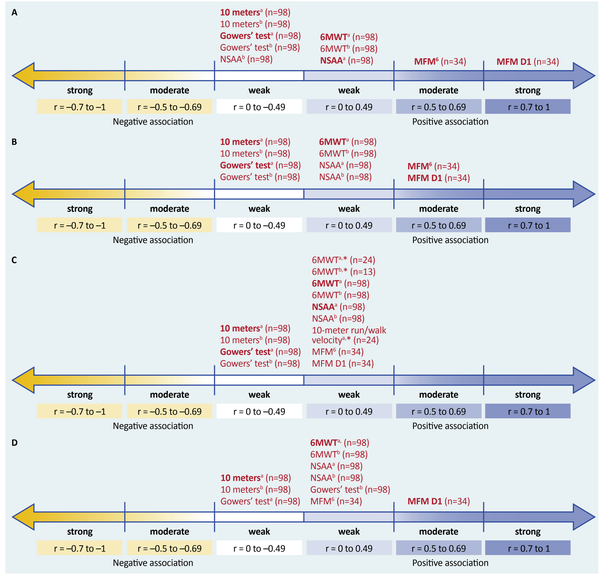
Figure 3. Correlations between functional measures and EQ-5D-5L in SMA and MQS



Reported associations are based on regression coefficients. **Bold** indicates a statistically significant indication.

- A moderate but statistically significant correlation was observed between EQ-5D-5L scores and FVC (R=0.521; *P*=0.0155) and maximum voluntary velocity (MVV; R=0.534; *P*=0.0126) (**Figure 3**).[2]
- Notably, significant correlations were only observed in adult patients with MQS.
- In the Gocheva *et al* 2019 study on DMD, both the Generic Core and Neuromuscular Model scales of the PedsQL–Child Self-Report (CRS) were weakly positively correlated with baseline scores from 6MWT, NSAA (GCS only) and moderately or strongly with motor MFM[6] (**Figure 4A–B**)

Figure 4. Correlations between functional measures (A) PedsQL GCS–CRS, (B) PedsQL NMM–CRS, (C) PedsQL GCS–PPR and (D) PedsQL NMM–PPR in DMD



Lower Gowers' test and 10-metre walk scores indicate improvements, hence negative associations to quality of life would indicate a benefit. Reported associations are based on Spearman's or Pearson correlation. **Bold** indicates a statistically significant indication. [a]Correlation of baseline data. [b]Correlation at change from baseline after 1 year. *Lack of information regarding significance.

- Baseline results from the 10MTWR and Gowers' test had a weak negative correlation with both scales of the PedsQL–CRS.[6]
- Similarly, the Generic Core and Neuromusclar Model scales of the PedsQL–Parent Proxy-Report (PPR) were positively correlated with baseline scores from 6MWT and NSAA (GCS) only[6] (**Figure 4C–D**)
  - Baseline results from the 10MTWR also had a weak negative correlation with both scales of the PedsQL–PPR.[6]
- When comparing PedsQL and PODCI to therapist-obtained clinical measures of disease severity in DMD, McDonald *et al* 2010 found that selected PODCI domains (specifically the transfers/basic mobility and sports/physical function scores) were more strongly associated with 10MWR, the Vignos lower extremity test, and walking velocity than the PedsQL–Physical Health subdomain score.[8]
- Houewen van Opstal *et al* 2014 did not observe any significant correlations between the KIDSCREEN-52 instrument and various physical function measures.[9]

Limitations

- This review was limited to studies published in English language. It is possible that relevant studies published in other languages were not retrieved.
- Unlike a systematic literature review, the present literature search was not subjected to a critical appraisal of the risk of bias. However, a targeted review approach can still be considered a rigorous and transparent method to synthesise evidence and provide insight into physician- and patient-reported associations.
- Another limitation is that the selected studies had different study designs (eg longitudinal vs cross-sectional) and used different methods for correlation analysis.
- Rare disease studies necessarily have smaller trial sizes, making statistical analyses more challenging.

Discussion

- Across various rare muscular and neurodegenerative diseases, statistically significant associations between physician-measured physical/functional outcomes and patient-reported QoL can provide insights on how functional gains impact patient experience.
- Analyses of correlations between physical functions and QoL can help address payer concerns when evaluating data from rare disease clinical trials about how a functional measure can be made more patient-relevant and meaningful. Demonstration of statistical associations will lend support to addressing concerns on the selection of appropriate and validated instruments for the disease state.
- Moreover, these approaches provide ways to model and potentially predict changes in QoL using functional-measure regressions where long-term data may be lacking.
- The review also highlights the customised use of instruments across diseases despite having functional features in common, which makes work to identify and interpret functional and QoL associations challenging. Prespecified correlation studies are worth considering in statistical analysis plans for clinical trials and may lend more credibility to functional and PRO results when interpreted by regulators and payers.

CONCLUSIONS

- Findings from the literature review showed that, across the various rare muscular, skeletal, and neurodegenerative diseases analysed, strong and statistically significant associations were found between physician-measured functional outcomes and patient-reported QoL.
- While meriting further validation, these associations can provide new insights on the multisystemic nature of these diseases and provide an approach for modelling QoL gains and patient outcomes.

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