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Functional, fatiguability and quality of life (QoL) endpoints for spinal muscular atrophy (SMA) clinical trials: Perception by health technology assessment (HTA) bodies and regulators and validation status

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BACKGROUND

- Clinical trials in spinal muscular atrophy (SMA) use various endpoints to assess muscle strength, fatigue/fatigability, and quality of life (QoL).
- Evaluation using appropriately chosen evidence-based assessments, can help determine treatment response and the impact on the natural history of SMA.

Objective

- This research is aimed to examine how health technology assessment (HTA) bodies and the Food and Drug Administration (FDA) evaluate the applicability of these endpoints in SMA clinical trials.

METHODS

- Appraisals of SMA and analogue disease, Duchenne Muscular Dystrophy (DMD), Spinal and Bulbar Muscular Atrophy (SBMA), Amyotrophic Lateral Sclerosis (ALS), treatments by the UK (National Institute for Health and Care Excellence, NICE), France (Haute Autorité de Santé, HAS), Germany (Federal Joint Committee, G-BA; Institute for Quality and Efficiency in Health Care, IQWiG), Canada's Drug Agency (CDA) were assessed to evaluate their acceptance of the Revised Hammersmith Scale (RHS), Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), 6-Minute Walk Test (6MWT), 32-item Motor Function Measure (MFM-32), Pediatric Quality of Life Inventory (PedsQL) and further QoL and fatiguability endpoints.
- *Ad hoc* searches on validation and minimal clinically important difference (MCID) were performed.

RESULTS

- Summary of appraisals of HTA bodies assessment are presented in **Table 1**.
- Summary of key findings on validation and MCID is presented in **Table 2**.

Functional endpoints in SMA

- All functional endpoints were validated.
- MCIDs were identified for: HFMSE (SMA type 2: 1.5; type 3: 2.4), RULM (estimated based on distribution-based approaches: SEM = 2.9; 1/2 SD = 6.4; 1/3 SD = 4.3) and 6MWT (calculated values ranged from 18 to 70m).
- HFMSE was considered validated by G-BA/IQWiG, HAS, CDA and appropriate for advanced SMA with limited mobility by CDA. G-BA/IQWiG rejected the MCID provided.
- RULM was considered appropriate for individuals ≥24 (CDA) or ≥30 months (HAS). G-BA/IQWiG rejected evidence on its validation and considered it less relevant than HFMSE.
- 6MWT was found relevant in SMA analogue diseases, however, its MCID was not accepted (G-BA/IQWiG), and impact of external factors could lead to bias (FDA).
- MFM-32 offered sufficient gradation to assess functional abilities (NICE), but longer trial duration was recommended (FDA).

Fatigue/fatigability and PRO endpoints

- PedsQL was considered validated (G-BA/IQWiG) and correlated with mobility status (CDA).
- Other endpoints were not mentioned in the evaluations.

TABLE 1 Summary of endpoint assessments by HTA and regulatory bodies

	NICE	G-BA/IQWiG	HAS	CDA	FDA
HFMSE	✓ Health benefits presented on scale were accepted (later-onset SMA)	✓ Reliable, validated, patient-relevant (SMA) ✗ MCID rejected (SMA) Responder analyses not accepted (SMA)	✓ Validated (SMA)	✓ Validated (content, construct; SMA) Test-retest and intra-rater reliability (SMA) Appropriate for patient with limited mobility (SMA)	✓ Recommended (SMA)
RULM	? Not stated	⚠ Complement to MFM-32 and HFMSE (in SMA less appropriate because of symptoms manifestation) ✗ Not validated Responder analyses not relevant	✓ Appropriate for aged ≥30 months, regardless SMA type (SMA)	✓ Adequate Internal consistency (SMA) Excellent inter-rater reliability in aged ≥2 years (SMA)	✓ Acceptable, clinically meaningful results
6MWT	? Not stated	⚠ Patient relevant, validated (DMD) ✗ MCID not accepted (DMD) Age-dependent	? Not stated	✓ Construct validity and test-retest reliability (SMA)	✓ Clinically meaningful (DMD)
MFM-32	✓ Gradation in the assessment of functional abilities (SMA) Enables efficacy assessment in SMA type 2 and 3	✓ Patient-relevant (SMA type 3) ✗ Arbitrary threshold for response in responder analyses Sub-domain responses should be reported	✓ Relevant and validated (SMA)	✓ Validated (convergent and known-groups validity, internal consistency) and reliable (SMA)	✓ Acceptable as primary endpoint (SMA) Longer trial duration recommended (SMA)
PedsQL	? Not stated	✓ Well-studied, sufficient, validated (SMA) No MCID	? Not stated	✓ Limited validity Neuromuscular Module correlates well with mobility status	? Not stated

✓ accepted; ⚠ partially accepted; ✗ not accepted; ? not stated

TABLE 2 Validation status and MCIDs of SMA endpoints

Correlated with the WHO motor milestones; captures progressively more difficult motor abilities Demonstrated discriminative groups validity by distinguishing between SMA type, ambulant status and current WHO functional score	**RHS** **MCID**: NA
Widely recognized and validated (incl. SMA children) Content validity and clinical meaningfulness explored in adults, but a significant floor effect found in these patients	**HFMSE** **MCID**: 1.5 for SMA type 2 2.4 for SMA type 3
Validated in both ambulant and non-ambulant patients; ceiling effect in up to a third of ambulant SMA type 3 (without upper limb weakness) and floor effect at least in a proportion of non-sitters	**RULM** **MCID**: 2.9, 6.4 and 4.3
Validated in ambulant adult SMA patients Validated and reliable test in ambulatory SMA patients	**6MWT** **MCID**: 18-70 m
Ongoing debate; validation demonstrated in neuromuscular disorders	**MFM-32** **MCID**: NA (2.5-3.9 for COL6 and LAMA2-RD)
Validated for SMA	**MFM-20** **MCID**: NA
Good internal consistency, high test-retest reliability, and an ability to differentiate between SMA groups with different disease severities (SMA-HI and subscales) Valid, relevant, and reliable for multifaceted patient-reported disease burden in older children, teenagers, and adults with SMA	**SMA-HI** **MCID**: NA
	FSS **MCID**: NA (reported in SLE, MS, RA)
Considered appropriate for use in cancer, used and validated in other chronic diseases	**FACIT Fatigue** **MCID**: NA
	Muscle strength **MCID**: NA
Established through input from experts and patients	**Endurance Shuttle Tests** **MCID**: NA (proposed in other conditions, e.g., COPD)
Construct in pediatric patients with SMA* Information provided by proxy-respondents; not equivalent to reported by the patient.	**PedsQL Neuromuscular module** **MCID**: NA (4.4-4.5 for the Generic Core Scales)
No validation in SMA; validated in other populations, demonstrating good reliability and validity (e.g. RA)	**PROMIS Fatigue** **MCID**: NA

*Validity of the PedsQL™ 3.0 Neuromuscular Module and the PedsQL™ 4.0 Generic Core Scales.

Validated, Ongoing debate/validated for analogue disease(s), Not validated for SMA or analogue disease(s).
NA: MCID in SMA not available

CONCLUSIONS

- **HTA and regulatory bodies generally considered functional endpoints in SMA trials to be relevant and validated. However, their perceptions varied by country, influenced by factors such as SMA type, patient age, and motor function status. While some endpoints like HFMSE and MFM-32 received broader acceptance, others such as RULM and 6MWT faced inconsistencies in validation or MCID acceptance.**
- **There was limited attention to fatigue/fatiguability and QoL measures, despite their relevance to patient experience. The absence of consistent MCIDs and robust validation further limits their use in appraisals.**

KEY TAKEAWAYS

Functional endpoints are central, but country-specific preferences impact their acceptability. RULM, HFMSE and MFM-32 are perceived mostly positive by HTA bodies.

Fatigue/fatigability and QoL endpoints in trial has shown promise but remain underrepresented, despite their clinical importance and HTA acceptance of these endpoints remain uncertain.

Choosing the right endpoint is context-dependent, requiring alignment with age, motor status, and expected treatment benefit.

Greater clarity on MCID thresholds and validation standards would enhance cross-national regulatory alignment.

Understanding the strengths and limitations of each endpoint helps inform clinical trial design and improve the chances of successful appraisal.

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ABBREVIATIONS 6MWT: 6-minute walking test; ALS: Amyotrophic Lateral Sclerosis; CDA: Canada's Drug Agency; DMD: Duchenne muscular dystrophy; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue Scale; FDA: US Food and Drug Administration; FSS: Fatigue Severity Scale; G-BA: Gemeinsamer Bundesausschuss (The Federal Joint Committee); HAS: Haute Autorité de Santé; HFMSE, Hammersmith Functional Motor Scale Expanded; HTA: health technology assessment; IQWiG: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); NICE: National Institute of Health and Care Excellence; MCID: minimal clinically important difference; MID: Minimal important difference; MFM: Motor function measure; SD: standard deviation; PedsQL: Pediatric Quality of Life Inventory; PROMIS: Patient Reported Outcome Measure Information System; QoL: Quality of Life; RHS: Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SBMA: Spinal and Bulbar Muscular Atrophy; SMA: spinal muscular atrophy; SMA-HI: Spinal Muscular Atrophy Health Index; WHO: World Health Organization.

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