Comparison of Clinical Outcome Assessments in Randomized Controlled Trials and Observational Studies for Amyotrophic Lateral Sclerosis: A Scoping Review

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BACKGROUND

- Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder that rapidly impairs motor neurons. This leads to progressive muscle wasting, difficulty in swallowing and breathing, and death within 2-3 years of onset, primarily due to respiratory failure.[1,2]
- Available medications slow disease progression, preserve functional ability, and improve quality of life (QoL) for patients, but do not cure ALS.[3]
- Clinical outcome assessments (COAs) are critical in ALS research as they quantify the functional and symptomatic impact of the disease. They provide a clinically meaningful measure of disease progression that biological or survival endpoints alone may not fully capture. Regulatory agencies recognize that COAs can serve as key endpoints for evaluation of treatment benefits.[4]
- COAs in ALS are conducted via clinician-reported outcomes (ClinRO) and patient-reported outcome measures (PROMs).
- Comparison of COAs between randomized controlled trials (RCTs) and observational studies is important to ensure interpretability and real-world relevance. However, robust evidence directly comparing COAs between RCTs and observational studies in ALS remains limited.

OBJECTIVES

- To identify COAs being used in RCTs and observational studies and determine any differences in COAs used according to study type
- To compare the effects of treatment on COAs used in RCTs and observational studies

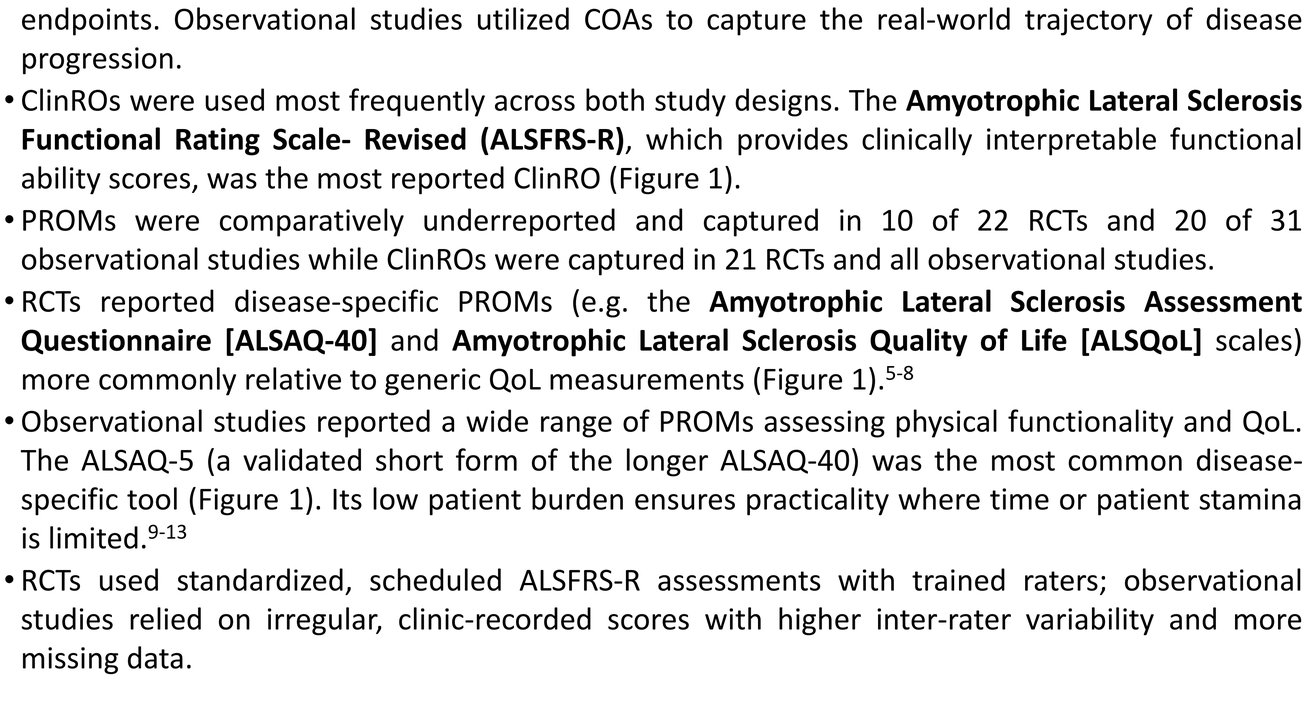
METHODS

- A scoping review was performed to identify relevant RCTs and observational studies assessing functional ability and QoL in patients with ALS.
- A PubMed and Embase search was conducted which included studies published up to May 2025. This was supplemented by a targeted search for relevant systematic literature reviews (SLRs).
- Data relating to baseline characteristics, functional rating scales, and QoL measures were extracted and compared across the two study designs.

RESULTS

- A total of 3,781 citations were screened. Twenty-two RCTs and 31 observational studies were identified.
- Similar COAs were used across both study designs. RCTs utilized COAs as primary and secondary endpoints. Observational studies utilized COAs to capture the real-world trajectory of disease progression.
- ClinROs were used most frequently across both study designs. The **Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised (ALSFRS-R)**, which provides clinically interpretable functional ability scores, was the most reported ClinRO (Figure 1).
- PROMs were comparatively underreported and captured in 10 of 22 RCTs and 20 of 31 observational studies while ClinROs were captured in 21 RCTs and all observational studies.
- RCTs reported disease-specific PROMs (e.g. the **Amyotrophic Lateral Sclerosis Assessment Questionnaire [ALSAQ-40]** and **Amyotrophic Lateral Sclerosis Quality of Life [ALSQoL]** scales) more commonly relative to generic QoL measurements (Figure 1).[5-8]
- Observational studies reported a wide range of PROMs assessing physical functionality and QoL. The ALSAQ-5 (a validated short form of the longer ALSAQ-40) was the most common disease-specific tool (Figure 1). Its low patient burden ensures practicality where time or patient stamina is limited.[9-13]
- RCTs used standardized, scheduled ALSFRS-R assessments with trained raters; observational studies relied on irregular, clinic-recorded scores with higher inter-rater variability and more missing data.

Figure 1: Overview of COAs Identified (No. of Studies)



Abbreviations: FVC=Forced vital capacity; MMT=Manual muscle testing; FSS=Fatigue severity scale, HADS=Hospital anxiety and depression scale; MYMOP-2=Measure Yourself Medical Outcome Profile, EAT-10=Eating Assessment Tool

RESULTS (Contd.)

- Treatment effects measured through various COAs were variable and inconsistently reported across both study designs. This made direct comparisons difficult (Table 1). Overall, RCTs demonstrated slowing of ALSFRS-R decline, but this finding was not consistently reproduced in observational studies.

Table 1: COAs in RCTs vs. Observational Studies

Study	RCTs	Observational Studies
Diversity of COA Instruments	• ALSFRS-R was used in 21 RCTs to evaluate patients' functional abilities. • PROMs were limited to only 10 RCTs out of which seven RCTs used two disease-specific measures (Figure 1).	• ALSFRS-R was used to assess functional ability in 31 observational studies. • A wider variety of PROMs were used to assess QoL. Eight studies used 2 disease-specific measures while 13 studies used generic tools (Figure 1).
Patient Population	• RCTs reported disease durations of 5.5- 32.4 months at enrolment. • Shorter disease duration at enrolment and possible subsequent slower functional status decline may lead to treatment efficacy overestimation.	• Observational studies reported disease durations of 15.5-62.7 months at enrolment. • Greater variation in disease duration at enrolment may be reflected in less consistent treatment effects versus those observed in RCTs.
Effect of Treatment on Functional Status & QoL	• Baseline ALSFRS-R scores ranged between 32.0-41.9. • An average decrease in ALSFRS-R scores by 2-3 points was seen. • The effect of intervention in improving QoL was studied in 3 RCTs.	• The baseline ALSFRS-R score ranged between 29.0-39.0. • Changes in ALSFRS-R scores were inconsistent and variable. • Changes from baseline in QoL were rarely captured.
Assessment Duration	24-64 weeks	26-104 weeks

DISCUSSION

- COAs are used consistently across both RCTs and observational studies. Many of the same tools are used across the study designs, which facilitates comparisons between trial results and real-world observations.
- RCTs showed a stable decrease in ALSFRS-R scores which was not consistently reproduced in observational studies. This may be due to stringent RCT inclusion criteria versus observational studies' reflection of a more heterogenous real-world population. Further research may clarify the drivers of this difference.
- COA results reported in observational studies were subject to higher risks of bias and may be less reliable overall than those reported in RCTs due to the differences in RCT versus real-world data collection methods.
- PROMs have been historically under-reported in ALS research, but the use, validation and routine collection of QoL-specific PROMs (e.g., ALSAQ-40 / ALSAQ-5, EQ-5D) is increasing. This reflects a more nuanced approach to treatment effect measurement.
- The comparison of treatment effects on COAs in ALS could impact further research such as cost-effectiveness modelling for any potential new ALS treatments. Model inputs may come from either type of study depending on model requirements and data availability. This makes an understanding of the differences in observed treatment effects and reasons behind them essential.

CONCLUSION

- Differences in population selection, assessment administration, and reporting limit the comparability of COAs between RCTs and observational studies.
- Standardization and continued increased incorporation of PROMs can contribute to eventual stronger evidence synthesis and support decision-making based on research such as cost-effectiveness modelling in ALS.

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