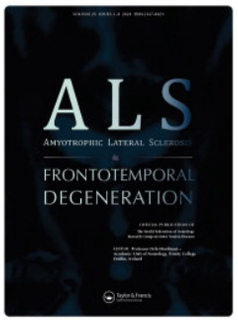

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MEETING REPORT

The ALSFRS-R Summit: a global call to action on the use of the ALSFRS-R in ALS clinical trials

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Abstract

The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) was developed more than 25 years ago as an instrument to monitor functional change over time in patients with ALS. It has since been revised and extended to meet the needs of high data quality in ALS trials (ALSFRS-R), however a full re-validation of the scale was not completed. Despite this, the scale has remained a primary outcome measure in clinical trials. We convened a group of clinical trialists to discuss and explore opportunities to improve the scale and propose alternative measures. In this meeting report, we present a call to action on the use of the ALSFRS-Revised scale in clinical trials, focusing on the need for (1) harmonization of the ALSFRS-R administration globally, (2) alignment on a set of recommendations for clinical trial design and statistical analysis plans (SAPs), and (3) use of additional outcome measures.

Keywords: *Clinical trial design, clinical trial outcome measures, functional rating scale, harmonization, statistical analysis*

Introduction

The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) was developed more than 25 years ago as an instrument to monitor functional change over time in patients with ALS (1). It was meant to be simple and administered by a trained individual via telephone for persons too advanced to attend clinic visits (before internet

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Table 1. The benefits and limitations of the ALSFRS-R discussed during the Summit.

Benefits	Limitations
• Simple and easy measure to use. • Provides consistent changes over time. • Can assess a patient's functional status remotely. • Excellent test-retest reliability when administered appropriately. • Can be used for prediction of disease course, survival, and efficacy of an investigational product. • There is a large data set available for modeling expected outcomes. • Correlates with changes in strength and quality of life. • Has been translated formally into multiple languages and has been used in clinical trials on multiple continents (this can also be a limitation). • Can provide a uniform assessment despite various presentations of the disease.	• It was not constructed using modern metric techniques, and a functional scale with improved metrics and improved reliability would be desirable. For example, the impact of a decline of 1 point is different between different items and between steps within an item. • Respiratory domain is not validated to the same extent as the other three domains. • Domains related to cognitive function and pain are not included. • Multiple translations globally have led to changes in meaning of questions when translated from English to specific languages. • Lack of version control within countries. In some countries, 10 language variants have been found. • Considerable variability in statistical analysis plans. • It remains unclear if the scale is linear in the early or late stages of ALS. • There is limited data on the scale in the later stages of ALS and as such the scale may not fully capture functional characteristics of later disease. • There is currently no universal set of SOPs, training, and certification. • Technological advances, such as mobile applications and wearable devices, have not been integrated into the scale; therefore, the scale does not assess high-level instrumental aspects of a patient's daily functioning. • Questions related to eating need to be altered to reflect eating utensils used in different regions around the world. We acknowledge there is a validated Japanese version that accounts for the use of chopsticks.

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; SOPs, Standard Operating Procedures.

use was widespread). A downside of the ALSFRS was the imbalanced contribution of the respiratory domain, which led to the scale being revised and extended with two items—resulting in the revised ALSFRS (ALSFRS-R) (2). Although these additional items appeared to add independent information to the scale, a complete re-validation of the entire revised scale was not performed. Other limitations arose as technology developed and the use of the ALSFRS-R expanded globally in the research and clinical setting (Table 1). Despite these limitations and the use of other clinical outcome measures in ALS trials (e.g., Forced vital capacity, patient reported outcomes, survival, time to event analysis and neurofilament), the ALSFRS-R remains the primary outcome measure required by regulators to assess the effect of a therapeutic intervention on the course of disease. In fact, the ALSFRS-R served as the basis of approval for two of the three most recently approved (by FDA) drugs for ALS and provided supporting data for the third (3).

To address uncertainties around the ALSFRS-R, we convened a global ALSFRS-R Summit with a working group of clinical trialists to discuss the strengths and weaknesses of the ALSFRS-R and explore a path forward to improve the use of the scale and determine alternatives. This essay presents the major themes that arose during the Summit. Our hope is that by sharing our perspectives we can stimulate a wider group of ALS clinical trialists to reflect on the use of the ALSFRS-R and join our call to action regarding the need for (1) harmonization of the ALSFRS-R administration globally, (2) alignment on a set of recommendations for clinical trial design and statistical analysis plans (SAPs), and (3) use of additional outcome measures.

Harmonization of the ALSFRS-R administration globally

With standardized administration and training, the test-retest reliability of the ALSFRS-R is >90%, supporting the fact that it is a reliable outcome measure (3). However, the scale is rarely administered consistently, due to a lack of harmonization in the administration, training and certification, and various translations of the scale.

We discussed administration of the scale and differences between the ALSFRS-R training standard operating procedures (SOPs) of the Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) led by the Barrows Neurological Institute (BNI; USA) and the Treatment and Research Initiative to Cure ALS (TRICALS; EU) program led by the University Medical Center (UMC) Utrecht in the Netherlands. In addition to NEALS and TRICALS, clinical research organizations are developing SOPs which adds to the variability. From a training and certification perspective, international studies that allow for multiple certifications for the ALSFRS-R can aggravate variability of the data. The training and certification that is in place differs across the key regions of use, namely, Japan, North America, and Europe. The respiratory questions are not consistently administered or trained across different drug development programs

resulting in individual raters having to use different instructions with patients in different clinical trials. This is a considerable challenge when raters are required to administer the ALSFRS-R in different ways on the same day, using different SOPs for each study (e.g., USA vs EU led clinical trials). Although only a small set of items have differences across the training SOPs, they are significant considering the lack of validation and the variability caused by the inclusion of the respiratory items. There was agreement that a uniform set of SOPs and operation manual is urgently needed to reduce the high risk of rater error and variability of scoring. This task was started in July 2022 when the NEALS and TRICALS leaders created a uniform set of administration SOPs specifically for the ALSFRS-R questions, responses, training, and certification. This document is being used for new clinical trials and we eagerly await its publication. However, further work including the Pan-Asian Consortium for Treatment and Research in ALS (PACTALS) is needed for full global representation. In addition, we believe training repeated at less than 2-year intervals will improve the reliability of assessment, along with certification/recertification of administration competency.

The differences in SOPs and training/certification are enhanced when clinical trials take place across countries with different languages. We have seen inconsistencies in translations of the scale and its administration instructions globally, while version control within countries adds to the issue (4). We discussed how the disparities in SOP instruction can be compounded by the changes in meaning of the questions when raters translate from English to specific languages. Administration of a question can influence the response to the question if the translation changes the question meaning and this can aggravate inter-rater variability. As an outcome measure in clinical trials, the variability introduced by the cultural and linguistic differences and effects needs to be addressed (5).

We believe that additional efforts to standardize administration, training/certification and translation of the scale globally will lead to a more robust, less variable outcome measure, increasing the confidence in the ALSFRS-R as a standalone or co-primary clinical trial endpoint. To push forward with the harmonization, the next steps would be for the NEALS and TRICALS leaders to,

- Develop a global training and certification program that includes PACTALS as a key stakeholder,
- Standardize translations, and,
- Be the custodians of the scale moving forward to ensure it remains a robust clinical assessment tool.

Alignment on a set of recommendations for clinical trial design and statistical analysis plans

We discussed the need to develop a more harmonized approach to clinical trial design and SAPs. From a clinical trial design perspective, we believe we need to look at new trial formats using ALSFRS-R, focusing on the improvement of adaptive trial designs in ALS. We acknowledge that we would need to come together as an ALS community and develop a strategy with patients, regulators, and regulatory advisory bodies (e.g., Critical Path Institute) to improve clinical trial design. The priority topics should be—primary and secondary outcome measures, increasing the use of patient reported outcomes, development of new, robust functional and biological outcome measures, how do you accurately measure change using an ordinal measure, validation of surrogate biomarkers and use as indicators of efficacy, and the optimal length of a clinical trial to fulfill regulatory requirements whilst being realistic for drug development. It will be vital to align globally on acceptable clinical trial designs and outcome measures for each phase, especially pivotal trials.

Since the respiratory domain in the ALSFRS-R was not validated in the same way as the rest of the scale, we discussed analyzing the ALSFRS-R data without the respiratory components as this may increase statistical power. Taking this a step further, we discussed whether other subdomains of the ALSFRS-R could be analyzed separately, rather than focusing on the total score. An advantage of subdomain analyses is that such analyses would be more sensitive if a therapeutic agent had a differential impact on each subdomain. Could subdomains that are more slowly changing be given less weight in the overall analysis? A potential disadvantage with subdomain analyses is that difficult to interpret patterns might emerge, such as the situation in which there was improvement in one subdomain but a deleterious effect in another. Lastly, if the respiratory domain as a whole is deleted, should it be supplemented with other respiratory measures, such as slow vital capacity?

We also considered the fact that technological advances have not been well integrated into the ALSFRS-R and may affect the assessment accuracy of a patient's daily functioning. Data was presented that indicated self-reported ALSFRS-R using a mobile device app was a reliable and valid option for the use of ALSFRS-R as an outcome measure.(6) In addition, questions related to eating need to be altered to reflect eating utensils across the world. Indeed, cross cultural validation is important, especially for international studies (5). However, it is important to acknowledge that regardless of the method used to collect data from the ALSFRS-R, they are all adapted forms of patient self-report and carry the inherent

Table 2. Additional clinical trial outcome measures discussed during the summit.

	Overview	Results
ALSFRS-RSE[7]	• Self administered questionnaire. • Uses a secure research application installed on participants' personal smartphones and used to deliver the ALSFRS-RSE at weekly intervals, or a web-based interface, used to deliver the ALSFRS-RSE to participants on their personal computer or mobile device at intervals of 1-3 months.	40 participant study • Correlates highly to the ALSFRS-R at baseline, month 3 and month 6 (Pearson R 0.96-0.97, 0.97, respectively). • Higher (2.86 points) at baseline, but the slopes of decline do not substantially differ vs the ALSFRS-R (-0.369 points/month) and ALSFRS-RSE (-0.475 points/month). 182 participant study • ALSFRS-RSE and ROADS correlate highly at 3 and 6 months (Cohen's kappa $\geq$71% ($p < 0.001$)). • The CV for functional decline on the two scales was similar at 6-months. • CV was higher for the ROADS at 3 months and lower at 12 months vs ALSFRS-RSE.
ROADS[8]	• A 28-question, self reported questionnaire using Rasch-built scales. • The scoring system includes scores from normal-2, abnormal −1 and unable to perform-0. • The result is provided as a total score.	• Improved targeting compared to the ALSFRS-R. • Test-retest reliability of 0.97. • Potential for improved sensitivity to change vs. ALSFRS-R.
D50 model[9,10]	• Summarizes each person's ALSFRS-R trajectory into a mathematically defined sigmoidal decay curve by iterative fitting of all available ALSFRS-R total scores. • The curve is defined by the decay time constant, and the turning point of the sigmoid at 50% loss of function is termed D50. • D50 is expressed as time in months from symptom onset until an individual reaches an ALSFRS-R score of 24 (i.e., 50% loss of function).	• D50 is highly linearly correlated to disease and can be used to quantify disease aggressiveness and local disease activity. • Strongly correlated with disease phases and *in-vivo* measures of cerebral structural integrity.
Kings Staging[11]	• Staging system • 5 stages assess disease progression from 1 (symptom onset) to 5 (death)	• 92% correlation with the ALSFRS-R. • Correlation with ALSFRS-R decreases when patient reaches Stages 4A and 4B. • Simple to apply. • Discrete stages of disease progression. • Stages occur in order with forward progression only. • Less vulnerable to misclassification vs ALSFRS-R.
AIMS	• Self administered 70-question questionnaire. • A factor analysis and Rasch modeling approach were used to develop three unidimensional scales for each functional domain: AIMS-Bulbar, AIMS-Motor, AIMS-Respiratory.	• Data was presented on the longitudinal trajectories and associations with survival for each domain (unpublished material).

Abbreviations: AIMS, Amyotrophic Lateral Sclerosis Impairment Multidomain Scale; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALSFRS-RSE, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised Self-Explanatory; CV, Coefficient of Variation; ROADS, Rasch-built Overall ALS Disability Scale..

limitations of such a collection method. Overall, there are many intrinsic issues that need to be managed in an SAP for the ALSFRS-R. A consensus is required on the best statistical approach across clinical trials. As a note, in the last 25 ALS clinical trials, over 20 different analytical strategies for the ALSFRS-R have been utilized (e.g., change analysis, modeling slope, and Bayesian analysis). A global conference involving academic and industry partners, statisticians, and regulators to discuss various analytic approaches could help a more harmonized approach to ALSFRS-R analysis.

Use of additional outcome measures

In this discussion we focused on a few key instruments (Table 2). The ALSFRS-R self-explanatory (ALSFRS-RSE) holds promise as a self-administered scale. It correlates closely with the traditional ALSFRS-R at baseline and across time (7), showing

less variability compared to the ALSFRS-R (likely due to the increased frequency of administration). The Rasch-Built Overall Amyotrophic Lateral Sclerosis Disability Scale (ROADS) is a functional outcome measure developed using a Rasch model and the patient themselves are the rater (8). As a result, there is less impact of rater interpretation misalignment and no impact of a change in rater. ROADS can be applied to both bulbar patients and limb onset patients. Direct comparison of the ROADS to the ALSFRS-RSE suggests that ROADS may be a measure more sensitive to changes in the progression of ALS (7). ROADS is currently under assessment in sponsor driven trials to build a dataset that will allow statistical modeling to be performed. The D50 model provides a sigmoidal abstraction of all available ALSFRS-R scores to separate overall disease aggressiveness from disease accumulation (9, 10). Disease aggressiveness (D50) is expressed as number of months since onset to lose 50% of function in the ALSFRS-R and can be used as a primary outcome measure. Normalizing a patient's disease trajectory to D50 provides an open individualized patient journey scale (rD50), defined as 0 at symptom onset, and 0.5 at 50% function loss. rD50 allows the comparison of events and biomarker observations between vastly different progression types which allows timing and sequence of clinical and biomarker milestone signals to be used as outcome measures. The King's and the MiToS staging systems are already being used in many ALS clinical trials (11). The variability that exists with the staging can be addressed by either an operation manual or clarity in the protocol and the rater training. The ALS Impairment Multidomain Scale (AIMS) was developed in the Netherlands and explicitly acknowledges the multidimensional nature of ALS by assessing each functional domain (AIMS-Bulbar, AIMS-Motor, AIMS-Respiratory). Challenges for AIMS will be how to derive global estimates for the treatment effect in RCTs. One option would be to weigh each domain according to patient preferences.

Where do we go from here?

Although the ALSFRS-R has proven to be a useful and valid outcome measure, it does have real-world shortcomings that need to be addressed to improve outcome measures for use in future clinical trials. To achieve this goal, we need the ALS community to come together and develop a consensus on how to move forward. We believe the next steps, at minimum, would be,

- A meeting of individuals from NEALS, TRICALS and PACTALS to develop a plan for global harmonization and administration.
- Evaluation of the research and regulatory requirements to support novel implementation of the ALSFRS-R, including the use of central raters, the ALSFRS-RSE, or AI-based delivery methods.
- A statistically driven conference aimed at exploring and potentially harmonizing the many approaches used to analyze the ALSFRS-R in clinical trials.
- A global effort to formally translate the scale into all available languages and to create training materials in every language possible to reduce variability in global trials and facilitate equitable inclusion in ALS trials globally and in countries with diverse populations.

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