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Title: Variability across versions of the self-administered ALSFRS-R: a review and call for harmonization

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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease predominantly affecting motor neurons resulting in substantial, progressive disability. The amyotrophic lateral sclerosis functional rating scale – revised (ALSFRS-R) is commonly used to assess and monitor functional status in patients with ALS. Additionally, it is the current regulatory accepted primary outcome measure documenting functional status in ALS clinical trials. The ALSFRS-R was originally designed to be administered to a patient by a trained professional. But over time it has been adapted to be performed independently by patients or their caregivers without assistance. Several different versions of the self-administered ALSFRS-R have been created over the past two decades, each with subtle but important differences. Some of these differences are related to language used in item wording or the platform for which the scale was intended to be administered (e.g. digitally). These differences across versions of the self-administered scale may be problematic as they could increase the heterogeneity of data collected across clinical trials or complicate interpretation of results across trials. Therefore, we highlight the need for a harmonized version of the self-administered ALSFRS-R to be used across all clinics and clinical trial sites internationally.

Keywords: ALS; motor neuron disease; clinical trials; outcome measures; patient reported outcomes (PRO)

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease predominantly affecting motor neurons (1). ALS results in substantial, progressive disability which is widely assessed clinically using the revised version of the ALS Functional Rating Scale (ALSFRS-R; 2). The ALSFRS-R is a clinician-reported outcome measure administered during an in-person visit via an expert-led structured interview. It is specific to ALS and includes 12 items, grouped into four domains, to assess bulbar symptoms, limb and trunk function, respiratory symptoms, and the need for non-invasive ventilation, tracheostomy with invasive ventilation, and percutaneous endoscopic gastrostomy (2).

Currently approved ALS medications, such as riluzole and edaravone, have at best a modest benefit (3). Tofersen, the first approved precision medicine therapy for SOD1 ALS, represents a hopeful development, but there is a profound need for improved disease modifying therapeutic options (4). There has been substantial growth in the number of clinical trials for novel ALS agents over the past decade. Given its broad acceptance, multi-dimensional perspective, and ease of use, the ALSFRS-R is the current regulatory accepted primary outcome measure documenting functional status in ALS drug development programs (5; 6).

Given the importance of the ALSFRS-R both in clinical care and clinical trial research, much effort has been directed at ensuring its validity, reliability, and reproducibility (7). Yet the current methods used to perform the ALSFRS-R have a number of significant challenges that create excessive variability in the data obtained for this critical primary outcome measure. This is compounded by the clinical heterogeneity across the ALS patient population, which in itself can pose a challenge for detecting any treatment effects in ALS clinical trials (8). This highlights the need for an outcome measure with optimized reliability.

Despite this recognition, inconsistencies have been identified in both the classification and description of items on the ALSFRS-R (9-11). This includes patient-reported difficulties selecting a discrete level of function based on the options provided (11). There have also been documented inconsistencies in repeat assessments and some specific aspects of the scale, particularly relating to the respiratory domain (12-13). Maier and colleagues noted the evolution of multiple variants of the scale, due to differential translation from English to other languages leading to different versions being used at different institutions (14). Finally, differences existed in ALSFRS-R training between the two groups responsible for most training in ALS clinical outcome measures: 1) the Northeast ALS Clinical Trials Consortium (NEALS) in the U.S. and Canada and 2) ENCALS/TRICALS led out of UMC Utrecht in The Netherlands. However, recently, an initiative driven by multiple leading ALS clinical researchers from those two groups proposed a harmonized standard operating procedure for administering the ALSFRS-R internationally (7). This harmonization for ALSFRS-R administration was designed to reduce response variability from center to center and has recently led to the publication of a unified standard operating procedure (7).

Move to Self-Administered Versions of the ALSFRS-R

Overall, in ALS, patient reported outcome measures (PROs) have emerged as new tools to gather key data efficiently and directly from patients (6; 14-15). These outcome tools are designed for patients to directly input their clinically relevant data without a clinician serving as interviewer or intermediary (16). Clinically, this has the potential advantages of allowing for digital collection of data remotely and more frequently, which could help notify the care team of any meaningful changes in symptoms or function, thus facilitating improved, timely care (16-21). A recent review examines many of the remote ALSFRS-R variants (22).

From a clinical research perspective, PROMs may reduce the burden placed on participants, increase frequency of data capture, reduce clinical trial costs, and reduce variability in data, and thus also potentially sample size (17; 19; 23). Heterogeneity in ALS-related data has been recognized as an important factor affecting clinical trial results and efficiency, thus potentially any efforts to reduce variability caused by our assessment tools may imbue benefits to ALS clinical trials (8). Therefore, the adoption of a self-administered ALSFRS-R has the potential for substantial benefits to both the provision of ALS care and administration of clinical trials.

Current Versions of Self-Administered ALSFRS-R

In the past two decades, several groups have published reports using self-administered versions of the ALSFRS-R or ALSFRS extended (ALSFRS-EX) (6; 14; 20; 24; 25). Many of these versions are included in a recent review (22). Overall, these self-administered versions appeared to demonstrate good inter- and intra-rater reliability with similar slopes of change when measured longitudinally and compared with the standard (i.e. clinician administered) ALSFRS-R (6; 25). In one report, the self-administered version of the ALSFRS-R featured superior within subject standard deviation compared to the standard scale (20).

The first study describing self-reported ALSFRS-R was in 2006 when Montes and colleagues reported a modified version of the ALSFRS-R with scale items specifically designed to be understandable to patients (26). For example, regarding speech, the ALSFRS-R answer item “Intelligible with repeating” was changed to “speech has changed; asked often to repeat words or phrases” (26). Sixty patients completed the self-administered version, alongside the standard clinician-administered version, twice with a three-month interval. They found the self-administered ALSFRS-R had a high level of reliability compared to the standard scale (ICC = 0.93, 95% CI: 088 to 0.96) and similar sensitivity to change over time compared to the standard scale (26). Results were similar when examining the self-administered ALSFRS-R completed by the caregiver as well. Patients and caregivers rated function higher than the clinicians, particularly across items assessing dressing, hygiene, and climbing stairs.

Another study described self-reported ALSFRS-R scores as rated by three different evaluators: 1) the patient, 2) the caregiver, and 3) a healthcare provider, with different healthcare providers serving as assessors to test for any meaningful impact of switching evaluators. (27). That study replaced medical terms such as “dyspnea” with “shortness of breath”, although no other substantive changes to the scale for use by patients (or caregivers) were reported (27). Patients (n=44) were assessed at 3-month intervals for a total of four visits. Similar to the earlier Montes et al (2006) study, they reported that patients tended to rate their function higher than caregivers or clinicians, but over the course of a 9-month follow-up period, they concluded each evaluator (i.e. different clinicians or patient self-report vs clinician) tracks similar magnitudes in ALSFRS-R score change from baseline to the fourth visit (27).

Subsequently, another group produced a different self-administered ALSFRS-R version, which was designed specifically for patients to complete independently, but also for use in digital applications (i.e. “apps”) and online platforms (6, 28, 29). This version included input from both patients and clinical experts, with subsequent feedback from those stakeholders incorporated into the final version. Self-administered ALSFRS-R item responses were modified to be answered in the first person, for example “Intelligible with repeating” was modified to “Sometimes I have to repeat things before people understand” (6). Patients completed the self-administered version on two occasions and compared with ALSFRS-R scores derived from the clinician scored version. Bakker and colleagues found their self-administered ALSFRS-R version demonstrated internal consistency (Cronbach’s coefficient alpha across domains ranging from 0.80 to 0.92) as well as excellent intra-rater (ICC = 0.97 for total score) and inter-rater (ICC = 0.97 for total score) reliability. Similarly high rates of reliability were found across individual ALSFRS-R domains (ICCs ranging from 0.94 to 0.97). Interestingly, the authors found a small systematic bias in which the patients tended to consistently rate their function slightly higher than the clinicians, by approximately 2 points of their total score (6).

In 2022, a research group in Germany published a new self-explanatory ALSFRS-R version, in the German and English language (14). This involved the evaluation of 10 different ALSFRS-R versions, including the original English version, six German language versions, two German language self-assessment versions, and one abbreviated version of the German ALSFRS-EX (14). A major change added for this version included “self-explanatory introductions” to each domain of the ALSFRS-R with the intention of aiding anyone completing the scale (i.e. patient, caregiver, and/or clinician) in its appropriate administration. This included instruction on how to account for limitations perceived to be caused by factors other than ALS or limitations present before the onset of ALS.

Additionally, changes were made to the explanations for certain answers choices. For example, for the ALSFRS-R item “intelligible with repeating” they modified the response on their self-administered scale to “Intelligible speech with repetition” and then added the additional explanation of “Frequent repetition of single words or parts of a sentence are required to convey meaning” to help patients understand if that answer choice was appropriate for their level of

function. The modifications in this self-explanatory version were intended to reduce the "room for interpretation" from the original ALSFRS-R version and to reduce the need for any training in the use of the scale. Beside the German-language version, an English version was published (14). The reliability and internal consistency of this new self-explanatory ALSFRS-R version is currently being assessed.

One rationale provided for the importance of developing a valid, reliable form of self-administered ALSFRS-R was to allow for collection of pertinent ALS functional data remotely, either through smartphone-based apps or internet-based interfaces (6; 20-21). This is aimed at improving the care team's access to high-quality, timely data that may improve care delivery and reducing the burden on patients for in-person clinical trial visits. Thus, this form of data acquisition has the potential to improve clinical care as well as clinical research, but it is only feasible with a reliable, valid version of the self-administered ALSFRS-R. One study showed the feasibility of this approach by employing a self-administered ALSFRS-R on an open-source smartphone-based platform (20). The details regarding which version of the self-administered ALSFRS-R were not reported. However, it was demonstrated that 1) self-administered smartphone-based ALSFRS-R scores correlated highly (r=0.93) with clinic-based ALSFRS-R scores, 2) self-administered ALSFRS-R scores showed a similar rate of progression to scores derived from the standard scales, and 3) self-administered scores showed a lower within subject standard deviation than their standard scale counterparts (20). Importantly, this reduced within subject variability has the potential to improve statistical power of any clinical trial to a certain degree (23). Of note, the only differences between clinic-based and smartphone-based scores were between swallowing (smartphone-based scores 0.4 points higher) and dressing and hygiene (smartphone-based scores 0.8 points higher; 20). However, overall, their study highlights the potential of smartphone-based ALSFRS-R data acquisition in support of clinical care and clinical trials.

Impetus for an internationally harmonized self-administered ALSFRS-R

The recent harmonization of the standard ALSFRS-R, led by TRICALS/NEALS, was an important development to improve the scale in traditionally delivered trials (7). A comparable, but different, process would benefit the self-administered ALSFRS-R, particularly in digital settings to lower the burden placed on patients and improve clinical trial efficiency. Although the various versions of self-administered ALSFRS-R summarized above appear to have comparably high reliability and consistency compared with the standard clinician-administered scale, some important questions and issues remain. Firstly, as demonstrated by the process underpinning harmonization of the standard ALSFRS-R, it is possible that small differences across tools (or the way tools are administered) can have important consequences regarding the resultant data (7). This includes considering how the medium may play an important role when comparing ALSFRS-R administered via phone, video, computer/smartphone application, or on paper. For example, digital literacy, access, and patient comfort may influence the successful adoption of any digital versions of the scale (22). And thus, comparing studies that use different forms of

self-administered ALSFRS-R may be unnecessarily complicated and any attempts to pool that data could result in increased heterogeneity, an issue already well established and understood to decrease clinical trial efficiency in ALS (8).

Additionally, there is a lack of peer-reviewed and validated self-administered ALSFRS-R versions in languages other than English, Dutch, and German. The Maier et al group highlighted how multiple translations can lead to a plethora of scale versions which were subsequently consolidated by this group (14). Addressing this issue on the front-end of any harmonization effort may be more efficient and obviate the need for consolidation in the future. However, it should be appreciated finding consensus across languages and institutions may be challenging, especially given multiple groups have already produced their own versions with preconceived rationales for choices of wording or phrasing.

It is unclear if any of the previously published self-administered ALSFRS-R versions are best suited for remote/digital use on a smartphone or computer-based platform. Given many research groups now have more experience with data collected in this manner (e.g. 20-21, 30), we may be better situated to determine what features are most desirable in smartphone-based app and how they may differ from a scale performed classically using a pen and paper or verbally over the phone. However, non-inferiority of smartphone-based assessment of a self-explanatory version of the scale compared to clinic ALSFRS-R assessment has been demonstrated (30). These results - in a German version of the ALSFRS-R - are encouraging for ALSFRS-R versions in English and other languages, since the self-explanatory ALSFRS-R brings the substantial advantage of requiring only a single scale and this simplicity is desirable. Moreover, an overarching goal of any harmonization effort should be aimed at producing such a scale, obviating the need for different scale versions administered by clinicians (or the need for different versions across different platforms.

Finally, harmonization of self-administered ALSFRS-R presents a unique opportunity to critically compare the previously created versions. This should allow researchers to develop a harmonized version adopting the most valued features of any versions while addressing any perceived shortcomings. At present there is no quantitative data to clearly show one version of the scale is superior to another. But a consensus-based harmonization process involving key international stakeholders may prove fruitful in developing a tool that incorporates the best features of each version. Ideally, creation of a harmonized self-administered ALSFRS-R by consensus can replace older versions of this metric, abolishing the need for different versions (e.g., clinician-administered or older self-administered versions).

Conclusions and Future Directions

Based on our analysis in this review, we conclude that a harmonized self-administered ALSFRS-R, which can be completed via digital platform (e.g. smartphone application) and available across multiple languages would be helpful for enhancing care for persons with ALS and improving our ability to collect high quality data efficiently for the purposes of clinical trials. We

hope such a harmonized version can replace older versions of this scale, simplifying the approach to obtaining functional rating of patients for trials or clinical care. We also conclude that studies completed in this space to date have demonstrated that the currently available self-administered versions provide data very similar to standard ALSFRS-R (20; 30).

However, important steps remain prior to wide adoption of this tool in clinical settings or across trial sites. A crucial next step should include harmonization of a consensus-generated self-administered ALSFRS, ideally adopting the strengths and addressing the perceived weaknesses of previous versions. And whilst there is a need to adopt a harmonized version developed through consensus, the actual process of achieving consensus will likely take time, resources, and significant discussion. Production of a broadly accepted harmonized version would entail a multi-step process involving key stakeholders, outlined below with brevity.

To appropriately harmonize, there is a major need for qualitative studies to provide a fulsome evaluation of the tool's language and patients' understanding of the adopted language/terminology used in the scale. This should include direct consultation and collaboration with patients including multiple rounds of cognitive interviews, focus groups and brainstorming sessions. Furthermore, development of any harmonized version will also require robust test-retest studies within patients, as well as patient vs clinician scored, as has been performed in other individual ALSFRS-R variants (6). There will need to be an appropriate effort to address the need to have this tool validated and available in multiple languages. This will include backward-forward translations to all languages/dialects intended to be users of this scale in language that is readable to those users. These steps will need to be repeated in different countries to ensure the validity of the translations with comparable reliability and validity. One "master" version of the scale will need to be maintained by an open-access institution, provides the translated versions and could facilitate accurate future translation into other languages.

Work towards these aims is currently ongoing including clinicians, academics, and industry leaders. Finally, efforts are forthcoming to promote acceptance of a self-rated ALSFRS-R with health authorities by initiating a formal qualification procedure of the final harmonized version of the scale as an endpoint for ALS clinical trials. This effort would ideally be spearheaded by large multinational ALS organizations, such as TRICALS, ENCALS, and/or NEALS that would employ a centralized version control and validated translation environment.

Given the value and increasing importance of PROs, we believe the self-rated ALSFRS-R will continue to grow in popularity as a key clinical trial outcome measure in the coming years. Thus, the importance of developing a harmonized version of that scale, valid across multiple nations/languages, has become apparent. We hope this review serves to highlight that need and help develop momentum for the work necessary for self-rated ALSFRS-R harmonization.

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