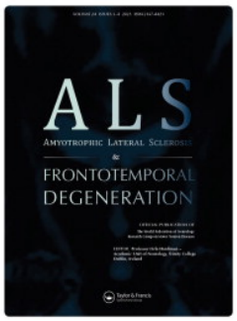

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iafd20

A qualitative evaluation of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) by the patient community: a web-based cross-sectional survey

Danielle Boyce, Michael Robinson, Jesse M. Cedarbaum, Lisa M. Shank, Christopher J. McDermott & Ruben P. A. van Eijk

To cite this article: Danielle Boyce, Michael Robinson, Jesse M. Cedarbaum, Lisa M. Shank, Christopher J. McDermott & Ruben P. A. van Eijk (2023) A qualitative evaluation of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) by the patient community: a web-based cross-sectional survey, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 24:3-4, 272-280, DOI: 10.1080/21678421.2022.2140592

To link to this article: https://doi.org/10.1080/21678421.2022.2140592

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2023; 24: 272–280

RESEARCH ARTICLE

A qualitative evaluation of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) by the patient community: a web-based cross-sectional survey

DANIELLE BOYCE[1], MICHAEL ROBINSON[2], JESSE M. CEDARBAUM[3,4], LISA M. SHANK[5], CHRISTOPHER J. MCDERMOTT[6] & RUBEN P. A. VAN EIJK[7,8]

[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Independent ALS Patient Advocate, Denver, CO, USA, [3]Coeruleus Clinical Sciences, Woodbridge, CT, USA, [4]Yale School of Medicine, New Haven, CT, USA, [5]Independent researcher, Glen Burnie, MD, USA, [6]Department of Neuroscience, The University of Sheffield, Sheffield, South Yorkshire, UK, [7]Department of Neurology, UMC, Utrecht Brain Centre, University Medical Centre Utrecht, Utrecht, the Netherlands, and [8]Biostatistics & Research Support, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands

Abstract

Objective: The revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) is the most commonly used outcome measure in ALS studies. The aim of this study was to identify potential limitations of the ALSFRS-R from the perspective of people living with ALS and their caregivers.

Methods: A web-based survey was developed by investigators, people living with ALS, and their caregivers, and shared across social media. For each item, participants were asked, "Can you think of a situation where you might not be able to answer this item accurately or that your answer might not reflect your abilities?" Responses were divided into two categories: criticisms that could be addressed in a manual or issues with the items/responses that would require measure modification.

Results: 57 participants (72% participants with ALS, 28% caregivers) responded to at least one item question, of which 71.9% expressed concern about at least one item. The most frequently identified items were speech, walking, and cutting food. Common criticisms were: language used is of a medical literacy level too high; item is situational; difficult to distinguish the difference between response choices; and the structure and/or underlying assumptions of the item makes it difficult to answer.

Conclusions: Several items of the ALSFRS-R were considered to inaccurately reflect the abilities of patients with ALS. The ALSFRS-R may need a revision to address these issues, preferably in co-development with people living with ALS and their caregivers, and/or alternate outcome measures should be considered for patients with ALS.

Keywords: *amyotrophic lateral sclerosis, clinical outcomes, measurement, qualitative study*

Introduction

The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) is an instrument for evaluating disease progression in people living with amyotrophic lateral sclerosis (ALS) (1). It is the most commonly used outcome measure in clinical trials for ALS to determine treatment efficacy (2), and its use has been recommended by the major regulatory agencies (3,4). Despite consistent demonstration of rates of disease progression across multiple studies over time (e.g. 5,6), the subjectivity of the scale is frequently criticized by patients (7,8). The scale has also been criticized for important psychometric limitations such as multi-dimensionality, non-linearity, poor construct validity, and potential floor and ceiling effects (9–11). Although clinicians have been surveyed to

Correspondence: Ruben P.A. van Eijk, Department of Neurology, UMC Utrecht Brain Centre, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands. Tel: +31 (0) 88 75 554 94. E-mail: r.p.a.vaneijk-2@umcutrecht.nl

Supplemental data for this article can be accessed online at https://doi.org/10.1080/21678421.2022.2140592

(Received 2 August 2022; revised 17 October 2022; accepted 21 October 2022)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2022.2140592

indicate what a clinically important change would be (12), no similar work has been done to establish what a meaningful change in ALSFRS-R would be to people living with ALS. Further, unlike many other clinical outcome assessments (COAs), the validation of the ALSFRS-R predates the FDA Clinical Outcome Assessment Qualification Program and was not subjected to the same scrutiny as other measures used today.

While heavily criticized for its use in the research context, the ALSFRS-R is considered a good predictor of overall survival (1,5), and is therefore typically assessed at every clinical visit. In addition to in-person clinical visits, the instrument has been validated for use via videoconference (13) and telephone (14,15); there are also multiple validated self-administered versions of the scale (e.g. 16,17).

People with ALS and the caregivers who so frequently interact with the ALSFRS-R are uniquely qualified to assess the instrument. In this study, therefore, we conducted a qualitative analysis of the ALSFRS-R by asking people living with ALS and their caregivers to evaluate the measure in detail.

Methods

This study was a cross-sectional survey with both quantitative and qualitative components. A web-based survey was conducted using SurveyMonkey from July 2021 to November 2021 to elicit input on the ALSFRS-R. People living with ALS and caregivers of people living with ALS or passed away from ALS older than 18 years were included. A link to the survey was posted on Twitter and shared throughout the ALS patient advocacy community along with a message that the survey could also be conducted via interview with the PI. The survey was also distributed through the European Organization for Professionals and Patients with ALS (EUpALS). The North Star Research Ethics Review Board deemed this study to be exempt (IRB #NB100024). Completion of the survey implied consent to participate.

Participants were asked questions about their demographics, their experiences with clinical research, and the ALSFRS-R. They were then presented with each item of the ALSFRS-R (see Appendix A for complete version of the questionnaire). The survey contained both closed-ended and open-ended questions. Due to the qualitative nature of the questionnaire, individuals were not required to respond to all questions. Individuals were included in this analysis if they replied to at least one question about the ALSFRS-R items. Descriptive quantitative data was summarized using IBM SPSS Statistics version 27. Qualitative data were analyzed using a thematic approach inspired by Grounded Theory, which results in the capture of themes instead of summary statistics (18).

Table 1. Participant characteristics ($N = 57$).

	M (*SD*) or *n* (%)
Age, *M* (*SD*)	52.4 (10.5)
Most recent ALSFRS-R score, *M* (*SD*)	33.1 (13.9)
Participant type	
Person with ALS	41 (71.9%)
Caregiver	16 (28.1%)
Gender	
Female	33 (57.9%)
Male	24 (42.1%)
Race/ethnicity	
White or Caucasian	55 (96.5%)
Hispanic or Latino	1 (1.8%)
Other	1 (1.8%)
Marital status	
Married	45 (78.9%)
Not married	12 (21.1%)
Country	
United States	45 (78.9%)
Germany	2 (3.5%)
United Kingdom	2 (3.5%)
Sweden	1 (1.8%)
Canada	1 (1.8%)
the Netherlands	1 (1.8%)
Australia	1 (1.8%)
Belize	1 (1.8%)
Holland	1 (1.8%)
Israel	1 (1.8%)
Portugal	1 (1.8%)

Results

A total 57 individuals responded to at least one relevant question about the ALSFRS-R; demographic characteristics of the sample are shown in Table 1. Participants reported that they have completed the ALSFRS-R with a doctor for standard of care visits ($n = 43$, 75.4%), with a doctor for research visits ($n = 28$, 49.1%), as well as other times such as for online studies ($n = 25$, 43.9%). A wide variety of methods for administering the scale was reported. Respondents stated that when administered the ALSFRS-R, they have experienced a doctor or nurse verbally asking each item ($n = 31$, 54.4%), completing the form by themselves as a patient ($n = 30$, 52.6%), as well as a doctor or nurse scoring the form without input from the patient ($n = 21$, 36.8%).

Thematic analysis

Of the 57 respondents, 71.9% expressed concern about their ability to accurately answer at least one item of the ALSFRS-R scale (Figure 1). While these qualitative comments are meant to be analyzed thematically, the median number of critically assessed ALSFRS-R items per respondent was 3. Most individuals had concerns about item 1

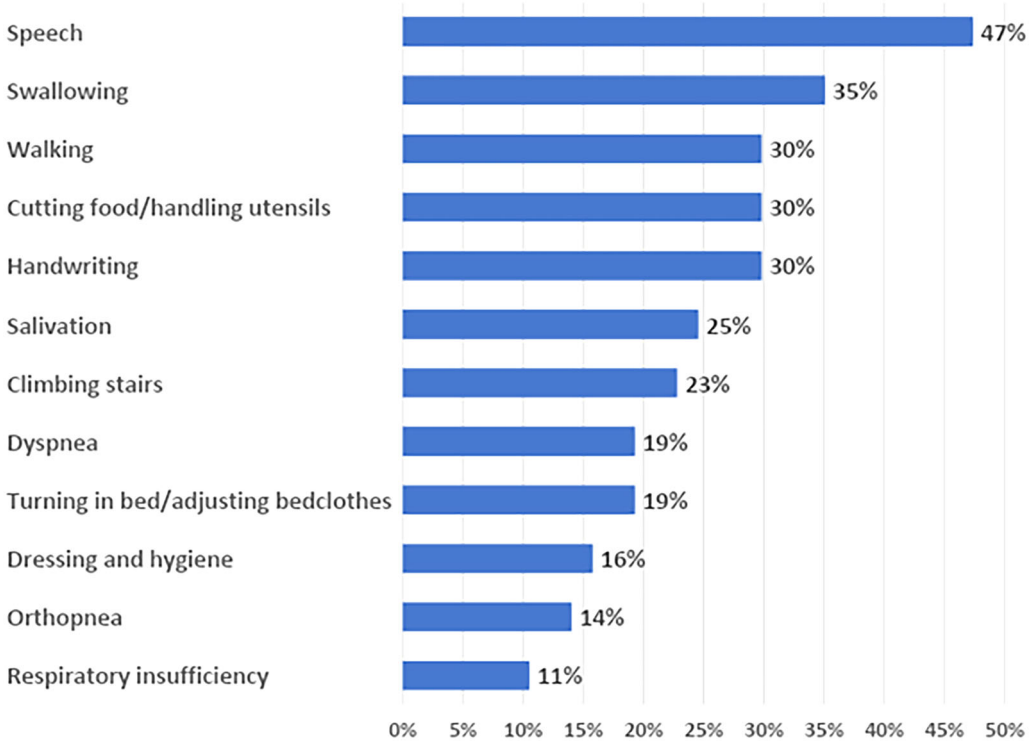

Figure 1. Percent of critiques by item in response to the question, 'Can you think of a situation where you might not be able to answer this item accurately or that your answer might not reflect your abilities?' Percentage is out of the total number of participants who responded to any question in this section ($n = 57$).

(speech; 47%), item 3 (swallowing; 35%) item 8 (walking; 30%), and item 5 (cutting food; 30%). The majority of comments fell into one of the following themes: language used in the item is of a medical literacy level too high for most non-clinicians; language used is of appropriate literacy level but needs clarity; the item is answered differently depending on the situation or equipment used; it is difficult to distinguish the difference between response choices on the scale; and the structure and/or underlying assumptions of the item makes it difficult to answer. The themes that emerged from this qualitative analysis are shown in Table 2, with exemplary quotes shown for each theme by item. For the complete data set used in this thematic analysis, see the Supplemental data file.

Language used in the item is of a medical literacy level too high for most non-clinicians

While this theme was not common, some responses to the swallowing and dyspnea items referenced that the language used in the item was of a medical literacy level too high for most non-clinicians. This is unsurprising, given that the original ALSFRS-R was not designed as a self-administered instrument and therefore contains language that a person living with ALS may not understand. For example, the term 'NPO' in the 'swallowing' item, which means 'nothing by mouth,' from the Latin *nil per os* is not commonly known outside of the medical community. Similarly, terms such as 'dyspnea' are likely unfamiliar to non-clinicians.

Language used is of appropriate literacy level but needs clarity

This theme emerged across several items: turning in bed and adjusting bedclothes, stairs, orthopnea, respiratory, and walking. For example, in the 'climbing stairs' item, participants could not identify what is meant by 'needs assistance', and questioned whether using a handrail constitutes 'assistance'. For the item, 'Turning in bed and adjusting bedclothes,' one response choice is 'Somewhat slow and clumsy, but no help needed.' One participant questioned what the threshold is for 'clumsy;' wondering if having difficulty turning in bed constitutes 'clumsy.'

The item is answered differently depending on the situation or equipment used

This theme emerged across numerous items: speech, walking, cutting food/handling utensils, dyspnea, and orthopnea. In particular, many respondents expressed concern that they would answer the 'walking' or 'speech' item differently early in the morning versus a long day of activity and speaking. With the assistive technology and equipment including specialized feeding utensils and handwriting support tools, respondents indicated the need for clarification and guidance for selecting the best response choice on the scale.

Table 2. Contextual themes by item based on qualitative responses.

Theme	Item	Exemplary quote
The question is answered differently depending on the situation or equipment used	Speech (Item 1)	'Time of day. Better in morning less intelligible in evening.'
	Walking (Item 8)	'Needs to allow for more options. Stairs? Uphill v downhill? Just getting up v walking for a bit?'
		'In water, I can 'cycle', bear some weight and move my legs freely. Out of water, I can only wiggle my toes. What # would that be: 4 or 5?'
	Cutting food/handling utensils (Item 5)	'I am able to feed myself finger foods. Sandwiches, pizza slices of fruit, etc. but unable to use utensils.'
		'Yes. Depends on specific food and utensil. My wife and use plastic utensils with foam tubing because they are light and easier to hold. How is she supposed to answer this? The score will depend on who is asking her and how they map her answer to one of these choices.'
	Dyspnea (Item 10)	'Yes. I don't get winded walking, but I do with doing ADLs.'
	Orthopnea (Item 11)	'What if I sleep just fine laying down on my side with 0 pillows but can't sleep in a sitting position. They categories can seem arbitrary at times.'
It is difficult to distinguish the difference between choices on the scale	Turning in bed and adjusting bedclothes (Item 7)	'yes The difference between the second and third choice is very unclear. Is the third choice implying that help is needed? What exactly is "can initiate" mean?'
		'Yea. This is a weird question. There's a lot in between the options.'
	Dyspnea (Item 10)	'I can't imagine how a responder picks between the last two items. Is the last option only for when mechanically ventilated and under what conditions – 24 hours a day? just at night?'
	Climbing stairs (Item 9)	'Too much happening between mild difficulty and needs assistance.'
	Walking (Item 8)	'There is a lot of room between early difficulties and walk with assistance. My son walks, with difficulty it doesn't need assistance. Surfaces are the issues.'
	Dressing (Item 6)	'answers 3 and 4 can get blurred.'
		'I have a great deal of difficulty deciding between #2 and #3, they are not mutually exclusive. If my spouse is not around, I can do everything by myself but she helps if she is there to conserve my energy!'
The structure and/or underlying assumptions of the question makes it difficult to answer	Handwriting (Item 4)	'legibility of handwriting may have nothing to do with ALS - the item needs to clarify that this is a CHANGE in handwriting that goes from legible in illegible. Someones handwriting may be illegible to begin with regardless of ALS.'
		'… how does one approach answering the options considering handedness and bilateral differences in the levels of weakness or deficit. How is one supported to answer? Based on handedness? Or based on weakest hand?'
		'Is there a distinction for handedness. I am left handed. What is my left hand is far more effected than my right hand. Then imagine the reverse. Does that mean the same person with a deficit that is greater in the dominant hand potentially score two different numbers? My right hand isn't impacted but my handwriting will be very bad. If I had total loss of use of left hand and was forced to use non-dominant hand - how do I score?'
	Swallowing (Item 3)	'Yes - answer b describes two different problems "early eating problems" which is very vague - too vague. What is an early problem versus a late problem? Clearly dieatary consistency may change before occasional choking events making it hard to respond to this question.'
	Turning in bed and adjusting bedclothes (Item 7)	'Turning and adjusting sheets are two entirely different activities. Because my legs are compromised, I have to move them with my hands. Adjusting sheets, on the other hand is not compromised in any way.'
	Orthopnea (Item 11)	'Some people (my wife included) always used multiple pillows and has had trouble sleeping unrelated to ALS.'
	Respiratory (Item 12)	'I might have Respiratory Insufficiency but have adapted by limiting my activity or changing my position and not need any additional intervention but I still have the deficit.'
	Salivation (Item 2)	'Ask about dry mouth as well as salivation.'
Language used in the question is of a medical literacy level too high for most non-clinicians	Dyspnea (Item 10)	'… stop using medical terms in the scale - need to use lay terms given the frequent self report nature of this use of this scale.'
	Swallowing (Item 3)	'Don't know what the last option (NPO) means'
Language used is of appropriate literacy level but needs clarity	Turning in bed and adjusting be dclothes (Item 7)	'I really struggle to understand when the threshold is met to answer "b". Yes, it's harder to turn in bed, but is clumsy? When does it become "clumsy" it's hard to interpret when to start selecting answer b'

(*Continued*)

Table 2. (*Continued*).

Theme	Item	Exemplary quote
	Stairs (Item 9)	'What do you mean by assistance?'
		'Yes. Needs assistance–is that the use of a handrail? This question should be revised.'
		'Very unclear as to what level of assistance is required to answer "needs assistance" - does that include using the handrail? Not clear as to what circumstances need to be to answer the assistance aspect of the response options and there seems to be a large gap in functional decline to go from needs assistance to cannot do … that is - the response options definitely do not appear to be linear.'
	Orthopnea (Item 11)	'Yes, I use a wedge, not sure if that counts as 2 pillows?'
	Respiratory (Item 12)	'Yes, Bipap is not an accurate term.'
	Walking (Item 8)	'"Early ambulation difficulties" is ambiguous. What does "early" mean and what does "assistance" mean? Does it mean I need a handrail on stairs or a walker? Do I put my hand on the wall to steady myself or hold onto furniture for security? Those aren't absolutely necessary but they do show a loss of skills in balance and ability and would they be considered "assistance"?'
		'Needs to allow for more options. Stairs? Uphill v downhill? Just getting up v walking for a bit?'
		'What's the different between early ambulatory difficulties and using a cane or walker? What is the patient refuses to use assistance, but really should have assistance? How do you answer that situation. Based on what the patient actually is doing, despite the majority of patients with the same level of deficits using assistance? This one is actually quite difficult to answer. I use assistance in many situations, but not all the time - so why do I answer?'
		'This question is unclear and is vague. What exactly is meant by early ambulatory difficulties.'

It is difficult to distinguish the difference between response choices on the scale

Many respondents expressed concern that they could not confidently choose between two of the response options on several items: turning in bed and adjusting bedclothes, dyspnea, climbing stairs, walking, and dressing. For example, with the 'Climbing stairs' item, one participant indicated that there is a fine line between the response choices, such as 'mild unsteadiness or fatigue' and 'needs assistance.'

The structure and/or underlying assumptions of the item makes it difficult to answer

This theme emerged across numerous items: handwriting, swallowing, turning in bed and adjusting bedclothes, orthopnea, respiratory, and salivation. Some respondents expressed concern that turning in bed and adjusting bed clothes are two separate concepts, and found it difficult to provide one response representing both activities. Another example of this theme is in the 'handwriting' item, specifically, the response choice, 'not all words are legible' is not worded in such a way that accounts for individuals who had illegible handwriting before their ALS diagnosis. An additional problem with handwriting was the concern that, if the dominant hand was unaffected, but the non-dominant hand was affected, the scale would fail to capture progression.

Discussion

This qualitative study demonstrates that, despite its historical utility, the ALSFRS-R may have important limitations in assessing the functional abilities of people living with ALS. We qualitatively highlight issues specific to individual items as well as overarching themes across items. These findings are of significant value as the ALSFRS-R is currently the most commonly used primary outcome in ALS clinical trials and may not fully capture the treatment effect experienced by patients. A joint effort between people living with ALS, caregivers, healthcare professionals, and regulators seems indicated to address the current limitations and move toward an improved patient-centered outcome.

Many of the limitations reported by people living with ALS and their caregivers were related to practical and linguistic challenges. These aspects can be easily resolved in administration manuals or standard operating procedures (SOP). Notably, the original ALSFRS-R administration manuals are not available. The lack of an official administration manual has led to a variety of SOPs and training programs, without clear global consensus on best practices. While ALSFRS-R certification and training programs for clinicians and researchers are available, they vary in their interpretations of how the scale should be used, such as the recall period and whether the administrator should provide cues to facilitate response selection. Similar issues exist for

patient-reported versions of the ALSFRS-R, where various research groups have independently developed their own patient version with different instructions of how to score the items (e.g. 16,19,20).

Global consensus on the scoring of the ALSFRS-R, with dedicated version control, is relatively straightforward to implement. Our study, however, has also indicated more troublesome limitations of the scale. For example, people living with ALS indicated that the scoring of speech depended on factors such as the time of the day and previous activities, smaller changes in speech that significantly impact the patient do not change the item score, and that difficulties with speech volume was a key symptom that is not reflected in the responses. Participants also noted that turning in bed and adjusting bed clothes represented two separate concepts, yet were being assessed in the same item. In addition, several items were flagged for difficulty choosing between response options. Many of these issues are less likely to be easily resolved by SOPs and potentially highlight true limitations of the response categories and items themselves. In order to overcome these short-comings, a dedicated effort is required to redevelop a valid measure of disability and daily functioning.

Given the ubiquity of the current ALSFRS-R, it is recommended that the field reaches consensus on scoring for the current version of the measure and provide adequate version control of the measure moving forward. It is also important for experts in the field and individuals living with ALS to work together to develop an SOP to address the straightforward observed issues, such as defining the length of the recall period and clearly operationalizing terms used in the instrument. Before these issues are resolved, researchers relying on patient self-report outside of the clinical setting may want to consider using a self-administered version of the ALSFRS-R, which has instructions that resolve some of the observed issues, instead of the original version meant for clinician administration.

Our findings also have important implications for future research focused on refining the ALSFRS-R and/or developing new measures of disability and daily functioning in individuals living with ALS. When creating or modifying items, it is essential to be mindful of how context such as time of day and equipment or caregiver support influences response. Clarifying language is necessary to be clear of the specific context. It is also important to clarify and specify the timing of the item in the context of the onset of ALS symptoms, such as 'as compared to before you had ALS symptoms', though it may be preferred to minimize the possibility of recall bias and avoid asking about situations before onset. It is essential to avoid double-barreled concepts, such as 'turning in bed and adjusting bedclothes.' Lastly, providing examples may help respondents differentiate between gradings in the response to items.

This study has several limitations. First, our results represent a relatively small, anonymous convenience sample of people living with ALS and their caregivers. The individuals who responded to our survey may have already had a negative opinion about the ALSFRS-R. Therefore, the percentage of patients that experienced a measure limitation may have been elevated compared to the general patient population. In addition, the survey was presented in English only; future studies should include translated materials to be more inclusive of an international audience using a more structured study design (e.g. sending survey invitation to well-defined cohorts). Notably, no official translations exist of the ALSFRS-R. Instead, different versions of the ALSFRS-R have been independently translated to and adapted for other languages (e.g. 21,22,23). It is important for future studies to examine the reliability, validity, and clinical relevance of the ALSFRS-R for these versions as well. We did not collect comprehensive demographic and clinical characteristics, and therefore could not distinguish between participants with different rates of progression and other important characteristics, such as cognitive impairments. We were unable to verify responses with clinical documentation. For caregivers, there was no limitation on how recently they cared for the person with ALS; this can introduce recall bias. Future, larger studies should address these concerns.

Conclusion

Almost three-quarters of the participants in this study indicated concerns that they might not be able to answer the items accurately or that their answers might not reflect their abilities. Though improving language may address some of these concerns, there also appears to be a need to critically revise items of the ALSFRS-R to accurately capture the functioning of the person with ALS. Alternatively, it may be important to consider developing other measures to better capture disability and daily life functioning in individuals with ALS. The observations reported here could also be useful in the evaluation of more recent (patient-reported) instruments such as the Rasch-built Overall ALS Disability Scale (ROADS) (24), MND Dyspnea Scale (MND-DS) (25) or Center for Neurologic Study Bulbar Function Scale (CNS-BFS) (26). When refining or developing relevant measures, it is important to involve people with ALS and/or caregivers in the process in order to develop valid items with thorough SOPs to improve measure reliability. With the ubiquity of the ALSFRS-R as a primary outcome measure of choice in clinical trials of experimental treatments

(4), our ability to discover new treatments may be in part hindered by our inability to accurately and reliably measure clinically meaningful changes in patient disability and functioning. The findings from this study suggest that we may need to prioritize our efforts to resolve these limitations in order to increase our chances of being able to accurately measure treatment benefit in clinical trials of new treatments for ALS.

Acknowledgements

The authors would like to thank the participants of this study. We would like to acknowledge the contributions of Mary C. Collet, MS and Phil Green, BS to the manuscript.

Declaration of interest

CJM is supported by the National Institute for Health and Care Research Sheffield Biomedical Research Center and a National Institute for Health and Care Research Professorship award. The authors report there are no other competing interests to declare.

ORCID

Lisa M. Shank http://orcid.org/0000-0002-6922-7946
Christopher J. McDermott http://orcid.org/0000-0002-1269-9053
Ruben P. A. van Eijk http://orcid.org/0000-0002-7132-5967

Data availability statement

The subset of the data that support the findings of this study have been included in a Supplemental file.

References

1. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999;169:13–21.
2. van Eijk RPA, de Jongh AD, Nikolakopoulos S, McDermott CJ, Eijkemans MJC, Roes KCB, et al. An old friend who has overstayed their welcome: the ALSFRS-R total score as primary endpoint for ALS clinical trials. Amyotroph Lateral Scler Frontotemporal Degener. 2021;22:300–7.
3. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis. London (UK): European Medicines Agency; 2016.
4. US Food and Drug Administration. Guidance for industry: amyotrophic lateral sclerosis: developing drugs for treatment. Silver Spring (MD): US Food and Drug Administration; 2019.
5. Kaufmann P, Levy G, Thompson JL, Delbene ML, Battista V, Gordon PH, et al. The ALSFRSr predicts survival time in an ALS clinic population. Neurology 2005;64:38–43.
6. Kollewe K, Mauss U, Krampfl K, Petri S, Dengler R, Mohammadi B. ALSFRS-R score and its ratio: a useful predictor for ALS-progression. J Neurol Sci. 2008;275:69–73.
7. @kelsieswrites. I think ALSFRS fails everyone. And I have no reason to believe the science won't bear out here, in the end. Just need a bit more time to study how trial participants do longer term. Thankfully this trial has a very robust OLE and so the data is there for @biogen to do that. ❤🙏 [Twitter]. 2021 Available at: https://twitter.com/kelsieswrites/status/1449919426917126145.
8. @alli_naquin. I am a pALS that has been excluded from drug trials due to "slow progression". How do we transition away from ALSFRS as the sole primary endpoint? Is this trial design hurting or helping the search for treatments? [Twitter]. 2021 Available at: https://twitter.com/alli_naquin/status/1450484302932856834.
9. Bacci ED, Staniewska D, Coyne KS, Boyer S, White LA, Zach N, et al. Item response theory analysis of the amyotrophic lateral sclerosis functional rating scale-revised in the pooled resource open-access ALS clinical trials database. Amyotroph Lateral Scler Frontotemporal Degener. 2016;17:157–67.
10. Franchignoni F, Mandrioli J, Giordano A, Ferro S, ERRALS Group. A further Rasch study confirms that ALSFRS-R does not conform to fundamental measurement requirements. Amyotroph Lateral Scler Frontotemporal Degener. 2015;16:331–7.
11. Rooney J, Burke T, Vajda A, Heverin M, Hardiman O. What does the ALSFRS-R really measure? A longitudinal and survival analysis of functional dimension subscores in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2017;88:381–5.
12. Castrillo-Viguera C, Grasso DL, Simpson E, Shefner J, Cudkowicz ME. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010;11:178–80.
13. Newton J, Jayaprakash K, Glasmacher SA, McEleney A, Bethell A, Fraser E, et al. Excellent reliability of the ALSFRS-R administered via videoconferencing: a study of people with motor neuron disease in Scotland. J Neurol Sci. 2020;416:116991.
14. Berry JD, Paganoni S, Carlson K, Burke K, Weber H, Staples P, et al. Design and results of a smartphone-based digital phenotyping study to quantify ALS progression. Ann Clin Transl Neurol. 2019;6:873–81.
15. Kasarskis EJ, Dempsey-Hall L, Thompson MM, Luu LC, Mendiondo M, Kryscio R. Rating the severity of ALS by caregivers over the telephone using the ALSFRS-R. Amyotroph Lateral Scler Other Motor Neuron Disord. 2005;6:50–4.
16. Bakker LA, Schroder CD, Tan HHG, Vugts S, van Eijk RPA, van Es MA, et al. Development and assessment of the inter-rater and intra-rater reproducibility of a self-administration version of the ALSFRS-R. J Neurol Neurosurg Psychiatry. 2020;91:75–81.
17. Montes J, Levy G, Albert S, Kaufmann P, Buchsbaum R, Gordon PH, et al. Development and evaluation of a self-administered version of the ALSFRS-R. Neurology 2006;67:1294–6.
18. Charmaz K. Constructing grounded theory: a practical guide through qualitative analysis. Thousand Oaks (CA): Sage Publications; 2006.
19. Manera U, Cabras S, Daviddi M, Vasta R, Torrieri MC, Palumbo F, et al. Validation of the Italian version of self-administered ALSFRS-R scale. Amyotroph Lateral Scler Frontotemporal Degener. 2021;22:151–3.
20. Wicks P, Massagli MP, Wolf C, Heywood J. Measuring function in advanced ALS: validation of ALSFRS-EX extension items. Eur J Neurol. 2009;16:353–9.
21. Guedes K, Pereira C, Pavan K, Valerio BC. Cross-cultural adaptation and validation of als Functional Rating Scale-

Revised in Portuguese language. Arq Neuropsiquiatr. 2010;68:44–7.
22. Maksymowicz S, Kukołowicz P, Siwek T, Rakowska A. Validation of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale in Poland and its reliability in conditions of the medical experiment. Neurol Sci. 2021; 42:943–9.
23. Rashed HR, Tork MA, Soliman R, Serag R, Fahmy N. Arabic adaptation and validation of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R): Egyptian study. Amyotroph Lateral Scler Frontotemporal Degener. 2021;22:220–2.
24. Fournier CN, Bedlack R, Quinn C, Russell J, Beckwith D, Kaminski KH, et al. Development and validation of the Rasch-built overall amyotrophic lateral sclerosis disability scale (ROADS). JAMA Neurol. 2020;77:480–8.
25. Helleman J, Kruitwagen-van Reenen ET, Bakers J, Kruithof WJ, van Groenestijn AC, Jaspers Focks RJH, et al. Using patient-reported symptoms of dyspnea for screening reduced respiratory function in patients with motor neuron diseases. J Neurol. 2020;267:3310–8.
26. Smith RA, Macklin EA, Myers KJ, Pattee GL, Goslin KL, Meekins GD, et al. Assessment of bulbar function in amyotrophic lateral sclerosis: validation of a self-report scale (Center for Neurologic Study Bulbar Function Scale). Eur J Neurol. 2018;25:907–e66. Epub 2018 Apr 16. Erratum in: Eur J Neurol. 2018 Oct;25(10):1303.

Appendix A

Survey questions

The purpose of this study is to document the attitudes of people with amyotrophic lateral sclerosis (ALS) and/or their caregivers toward the ALS Functional Rating Scale – Revised (ALSFRS-R).

The survey is anonymous. It has been reviewed by an Institutional Review Board.

You can discontinue the interview at any time if any of the questions make you uncomfortable. You do not have to answer any questions that you would rather not answer. There will be no penalty if you withdraw or do not fully answer any questions.

If you prefer to provide your responses in a video chat or phone interview, please contact Danielle Boyce, MPH, Principal Investigator at db902888@wcupa.edu to schedule.

- What is your age?
- I am
  - Male
  - Female
  - Other

Prefer not to answer

- Which of the following best describes your race/ethnicity?
  - Asian or Pacific Islander
  - Black or African American Hispanic or Latino
  - Native American or Alaskan Native White or Caucasian
  - Other (please specify)
- Which of the following best describes your relationship status?
  - Married
  - Widowed
  - Divorced
  - Separated
  - In a domestic partnership or civil union Single, but cohabiting with a significant other Single, never married
- In what state or territory do you live?
- If you live outside of the United States, where do you live?
- I am a:
  - Person with ALS
  - Caregiver of someone who has or had ALS
- (for people with ALS)
  - Date of ALS symptom onset (month/year)
  - Date of ALS diagnosis
  - Do you know your ALSFRSR score?
- (For caregivers)
  - Please describe your relationship with the person with ALS
  - Do you know the most recent ALSFRS-R score for the person you care for?
- Have you (or the person you care for) ever participated in a clinical trial or other research project?
  - Yes
  - No
  - (If yes): Please describe your study participation
- Please review the ALSFRS-R document here: https://www.outcomes-umassmed.org/als/alss-cale.aspx
- Have you ever completed this form before?
  - Yes
  - No

Unsure

- If yes: When have you completed this form? (check all that apply)
  - At the doctor's office or via phone or telehealth visit with the doctor for standard of care visits
  - At the doctor's office or via phone or telehealth visit with the doctor for research visits
  - At other times, such as online studies
  - Please describe
- How is the information on the form documented? (Check all that apply)
  - The doctor or nurse asks me questions about each item, and we come up with the right number together
  - The doctor or nurse scores the form without my input
  - I fill it out myself
  - Other (please describe)
- Now we will review each item in the ALSFRS-R and ask for your thoughts. If you don't have any thoughts or concerns about an item, that's totally fine.
  Can you think a situation where you might not be sure not be able to answer this item

accurately or that your answer might not reflect your abilities? Please describe.

1. Speech
- Normal speech processes
- Detectable speech disturbance
- Intelligible with repeating
- Speech combined with nonvocal communication
- Loss of useful speech

2. Salivation
- Normal
- Slight but definite excess of saliva in mouth; may have nighttime drooling
- Moderately excessive saliva; may have minimal drooling
- Marked excess of saliva with some drooling
- Marked drooling; requires constant tissue or handkerchief

3. **Swallowing**
- Normal eating habits
- Early eating problems-occasional choking
- Dietary consistency changes
- Needs supplemental tube feeding
- NPO (exclusively parenteral or enteral feeding)

4. Handwriting
- Normal
- Slow or sloppy; all words are legible
- Not all words are legible
- Able to grip pen but unable to write
- Unable to grip pen

5. Cutting food □ with gastrostomy
- Normal
- Somewhat slow and clumsy, but no help needed
- Can cut most foods, although clumsy and slow; some help needed
- Food must be cut by someone, but can still feed slowly
- Needs to be fed

6. Dressing and hygiene
- Normal function
- Independent and complete self-care with effort or decreased efficiency
- Intermittent assistance or substitute methods
- Needs attendant for self-care
- Total dependence

7. Turning in bed
- Normal
- Somewhat slow and clumsy, but no help needed
- Can turn alone or adjust sheets, but with great difficulty
- Can initiate, but not turn or adjust sheets alone
- Helpless

8. Walking
- Normal
- Early ambulation difficulties
- Walks with assistance
- Non-ambulatory functional movement only
- No purposeful leg movement

9. Climbing stairs
- Normal
- Slow
- Mild unsteadiness or fatigue
- Needs assistance
- Cannot do

10. Dyspnea
- None
- Occurs when walking
- Occurs with one or more of the following: eating, bathing, dressing (ADL)
- Occurs at rest, difficulty breathing when either sitting or lying
- Significant difficulty, considering using mechanical respiratory support

11. Orthopnea
- None
- Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows
- Needs extra pillow in order to sleep (more than two)
- Can only sleep sitting up
- Unable to sleep

12. Respiratory insufficiency
- None
- Intermittent use of BiPAP
- Continuous use of BiPAP
- Continuous use of BiPAP during the night and day

- Invasive mechanical ventilation by intubation or tracheostomy
  - Final question: can you think of any body parts or functions that are not addressed with the ALSFRS-R? Please describe.
  - If you have any questions about the survey, please contact Danielle Boyce, MPH, principal investigator, at db902888@wcupa.edu.