INTERNATIONAL ALLIANCE OF ALS/MND ASSOCIATIONS

Optimizing Clinical Trials: Outcome Measures for ALS/MND

October 2022 Roundtable

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Executive Summary

On October 6, 2022, a multi-stakeholder group, representing various communities within the International Alliance of ALS/MND Associations' network, gathered for a Roundtable focused on developing principles for optimizing clinical trial endpoints for ALS/MND. The goal of the effort is to advance efforts for optimizing the use of current endpoints (primarily the ALS-FRS-R) while aligning on additional endpoints that can be acceptable to regulators, trial sponsors, clinicians, and people living with ALS/MND.

The Roundtable encompassed an opening plenary, and two group discussions. The plenary session included a series of brief expert presentations designed to provide context about the history of the current ALS-FRS-R, updates about progress stemming from multiple recent activities on this topic, and descriptions of additional outcome measures for potential future use. Each expert presentation stressed the importance of engaging perspectives of those living with ALS in any effort to refine current outcome measures and develop new ones for the future. During the group discussions, participants were invited to 1) help shape principles for the Alliance on this topic and 2) to develop a list of recommended action steps for the community to undertake in advancing this effort.

Attendees

Meeting participants included representatives from multiple global ALS/MND organizations, members of the Alliance's staff and PALS and CALS Advisory Council (PCAC), industry officials and invited expert speakers. Global regulators from multiple countries were invited but unable to attend. All sessions were facilitated by Wendy Selig, Founder and CEO of WSCollaborative, and sponsorship support for the Roundtable was provided by Amylyx, Apellis, Biogen, Cytokinetics, and Mitsubishi Tanabe Pharma.

Attendee Roster - Discussion Group 1			
Last Name	**First Name**	**Affiliation**	**Country**
Bayerlin	Nancy	Mitsubishi Tanabe Pharma	USA
Blanchard	Angelie	Alliance	Canada
Boyce	Danielle	John Hopkins Medicine	USA
Cameron	Shae	Alliance	Canada
Cedarbaum	Dr. Jesse	Yale School of Medicine	USA
Cummings	Cathy	Alliance	Canada
Dave	Kuldip	Scientific Advisory Council (SAC)	USA
De Valck	Dirk	EUpALS	Netherlands
Fradette	Stephanie	Biogen	USA
Fournier	Dr. Christina	Emory University	USA
Green	Phil	PALS and CALS Advisory Council	USA
Mabe	Jessica	Alliance	Colombia
Manuel	Machelle	Amylyx Pharmaceuticals	USA
Matla	Andrea	ALS Patients Connected	Netherlands
Moore	Tammy	ALS Society of Canada	Canada
Mulcahy	Maxwell	Apellis Pharmaceuticals	USA

Nyberg	Sophie	MNDA UK	UK
Reviers	Evy	ALS Liga Belgium	Belgium
Robinson	Corey	Apellis Pharmaceuticals	USA
Ruiz	Orlando	ACELA	Colombia
Sane	Hemangi	Asha Ek Hope Foundation	India
Selig	Wendy	WSCollaborative	USA
Selness	Dan	Mitsubishi Tenabe Pharma	USA
Sigurdsson	Gudjon	MND Iceland	Iceland
Taylor	David	ALS Society of Canada	Canada
Timmons	Jamie	Amylyx Pharmaceuticals	USA
van der Lit	Angelique	PALS and CALS Advisory Council	Netherlands
van der Meijden	Conny	ALS Patients Connected	Netherlands
van Eijk	Dr. Ruben	University Medical Centre Utrecht	Netherlands
Zaveri	Nadia	Apellis Pharmaceuticals	USA

Attendee Roster - Discussion Group 2			
Last Name	**First Name**	**Affiliation**	**Country**
Abrams	Wendy	Honorary member	USA
Agnese	Wendy	Biogen	USA
Balas	Calaneet	The ALS Association	USA
Blanchard	Angelie	Alliance	Canada
Cameron	Shae	Alliance	Canada
Cummings	Cathy	Alliance	Canada
Fournier	Dr. Christina	Emory University	USA
Labib	Louna	Cytokinetics	USA
Mabe	Jessica	Alliance	Colombia
Nava	Armando	Fyadenmac	Mexico
Pauls-Backman	Andrea	Les Turner ALS Foundation	USA
Pomerantx	Mary	Cytokinetics	USA
Rudnicki	Stacy	Cytokinetics	USA
Selig	Wendy	WSCollaborative	USA
Sheehan	Bec	FightMND	Australia
Solano	Juan Marcos	ACELA	Colombia
Thomas	Gethin	MND Australia	Australia
Woff	Dr. Andrew	Cytokinetics	USA

Agenda

Optimizing clinical trials: Outcome measures for ALS/MND
October 6, 2022

Agenda Overview	
Plenary Session	Virtual
	October 6, 2022: 7:00am-8:30am ET New York
Group Discussion	Virtual
	Group 1; October 6, 2022; 9:00am-10:30am ET (New York)
	Group 2; October 6, 2022; 7:00pm-8:30pm ET (New York)

Agenda Detail

Plenary: Thursday October 6: 7:00-8:30am ET (New York)

- Contextual overview **Cathy Cummings** **(10 mins)**
- Optimizing ALSFRS-R
  - Clinician perspective – **Dr. Jesse Cedarbaum & Dr. Angela Genge (20 mins)**
  - Patient perspective – **Dr. Danielle Boyce & Phil Green** **(10 mins)**
- Looking ahead: Options for additional/better measures in the future
  - ROADS and telemedicine **Dr. Christina Fournier** **(15 mins)**
  - Adressing multi-dimensionality **Dr. Ruben van Eijk** **(10 mins)**
- Industry perspective **Stephanie Fradette (Biogen)** **(10 mins)**
- Wrap up & discussion groups plan **Wendy Selig** **(15 mins)**

Group Discussion
Virtual: Thursday, October 6; Group 1: 9-10:30am ET: Group 2: 7-8:30pm ET

Debrief from Plenary

Facilitated Discussion: Opportunities for improvement

Wrap up and Next Steps

The outcomes of the Optimizing Clinical Trials: Outcome Measures for ALS/MND Roundtable meeting are embedded in the document that follows.

Background

Alliance Executive Director **Cathy Cummings** provided the background and context for the Roundtable, noting the topic of outcome measures for ALS/MND clinical trials is timely and high relevant to the global community given recent regulatory actions to approve two new therapies for treatment of ALS, and multiple ongoing studies evaluating additional potential treatments. She referenced multiple recent meetings and discussions about this subject among various stakeholder groups, leading to an opportunity for the International Alliance, in its role as an "information gateway" among all the relevant parts of the ALS/MND global community, to convene a collective conversation.

She challenged the meeting participants to consider how all stakeholders can collaborate in advancing tangible action steps that will improve opportunities for people living with ALS/MND by optimizing clinical trials. Despite living in an "imperfect world" with an imperfect understanding of ALS/MND, there are ways to optimize current clinical trial outcome measures while designing additional and potentially better measures for the future. She cautioned against thinking about this topic in "binary" terms ("good vs. bad"), noting that any potential clinical outcome measure will have its pros and cons.

Expert Presentations:

Optimizing ALSFRS-R: Clinician Perspective -- Drs. Jesse Cedarbaum & Angela Genge

The meeting began with presentations from ALS clinicians. **Dr. Jesse Cedarbaum** of Yale School of Medicine (US) provided a brief history of development and evolution of the ALS-FRS-R scale to evaluate ALS disability. In the 1990's when the ALS-FRS scale was first developed, many studies were relying on quantitative muscle testing using overall survival as the gold standard clinical trial endpoint. Initially, the goal was to develop a questionnaire-based scale to record performance on activities of daily living that could complement quantitative muscle testing and would be easy to administer. The results of the questionnaire roll up into a single number rating designed to represent all variations of the clinical course of ALS. Having a single number was viewed as important to meet concerns among statisticians evaluating clinical trials.

Over time, in using the early ALS-FRS scale, it became clear that the scale was missing an important component relating to respiratory function. To address this gap, the scale was revised (ALS FRS-R) to include 12 items and a factor analysis across four domains: fine motor, gross motor, bulbar, and respiratory. Clinical relevance is currently defined as a 25% change in the rate of decline.

There are positive attributes to the ALS FRS-R as an outcome measure, including that it correlates with other measures, is flexible with respect to how it can be administered (and has been validated for the phone, online, in-person, self-administration). It also does reflect patient function and it has been used as a basis for approval of two new therapies for treating ALS.

On the downside, Dr. Cedarbaum noted that, although the intent was for a simple tool that could avoid ambiguity and interpretation, it has become clear that this has not been the case. Over time significant inter-patient variability has been noted and the respiratory domain correlates poorly with the other domains.

Additionally, the wording of some of the items is not consistent with current practice or use of technologies and can be confusing to patients.

While there is currently no recognized authoritative group taking ownership and being responsible for oversight of the scale use and appropriate updates, Dr. Cedarbaum noted that new outcome measure scales should be kept up-to-date and reflect the way people live their lives. He emphasized the importance of evaluating any future ALS outcome measures against quantitative muscle testing (QMT) and finding ways to generalize study results across a broad ALS population.

Dr. Angela Genge, of Montreal Neurological Institute (Canada), began by noting that while regulators recommend that any primary outcome measure in an ALS clinical trial should have a measure of function, they do not specify that it must be ALS FRS-R. That said, ALS FRS-R has been used in ALS clinical trials for several decades, creating a wealth of data to help sponsors model clinical trials and pointing to a variety of opportunities to improve its use.

Dr. Genge pointed to several problem areas in the use of ALS FRS-R. The first involves multiple variations in how it can be analyzed. There is a need to reduce the number of approaches to improve ability to compare between trials. She described a recent step forward in this direction as two groups in North America and Europe came together this summer to align and unify their standard operating procedures (SOPS) for training in evaluation of ALS FRS-R. A second important issue in optimizing use of ALS FRS-R pertains to the need to use the same rater for the duration of a clinical study to minimize variability in assessment. Given the impact that COVID has had on the entire clinical trial ecosystem and infrastructure, this requirement has been difficult to meet given the tremendous turnover among study coordinators and other clinical trial personnel. Finally, she noted variability among how various individuals interpret or agree with a patient's response to an item they are recording. This issue can be mitigated by having the scale be self-administered by the patient at home. While there is bias in how a patient answers the questions, this bias will be consistent over time.

Optimizing ALS-FRS-R: Patient Perspective -- Dr. Danielle Boyce & Phil Green

In providing the patient perspective, **Dr. Danielle Boyce** of Johns Hopkins University (US) described her recent work in evaluating how people living with ALS feel about the ALS FRS-R and its meaningfulness to their experiences. Through surveys of people with ALS and their caregivers, Dr. Boyce developed quantitative and qualitative evaluations of the ALS FRS-R, identifying several important shortcomings from the perspective of people directly impacted by the disease pointing to opportunities to improve the instrument. One area of criticism that emerged from this effort was the need to better define and standardize the categories in the scale. Opportunities also exist to provide greater clarity about the items within the scale, including revising the wording to make them easier to understand and reduce confusion. Patients noted that their answers to the questions in the instrument may vary depending on time of day, and they also may have difficulty determining a level of decline as they struggle to recall their previous abilities. It also can be difficult to distinguish the difference among response choices, or understand the underlying assumptions of a question, making it difficult to answer.

Several examples Dr. Boyce cited include speech, which can vary depending on the time of day, what or when the person eats or drinks. Legibility of handwriting may have nothing to do with ALS. It can be difficult to answer some questions when considering handedness and bilateral differences in the levels of weakness. Dressing and hygiene are also complex to evaluate, considering that if one's spouse is not around, the patient can do

everything alone, but it helps if the spouse is there to conserve energy. Turning and adjusting sheets are two entirely different activities for someone whose legs are compromised. Questions arose about evaluating need for assistance with walking. Does it mean the person needs a handrail on stairs or a walker or is it just a hand on the wall for balance? Overall, Dr. Boyce stressed that it can be extremely frustrating for a person with ALS knowing that so much is hanging on the ALS FRS-R score.

Building on Dr. Boyce's overview, **Phil Green**, a person living with ALS (US), emphasized the importance of this topic to the entire ALS community. When a person is first diagnosed with ALS, they usually have no idea what scales or measurement tools are used to track progression, but over time people quickly become experts in the disease and eventually fully understand what their ALS FRS-R number is and the nuances of how variations in answers to the questions can impact scores.

Phil stressed the need to focus on what is meaningful to people living with ALS, and he noted that several aspects of the ALS FRS-R are either out of date or miss the mark in terms of meaningfulness.
For example, evaluating handwriting and ability to hold a pen is not relevant to someone who never had good handwriting and almost never writes anything by hand. More relevant would be to measure typing ability and use of a computer or cell phone keyboard as these are actual functions of daily living for most people today.

Regarding the aggregate scores and changes that are viewed by the clinical and regulatory communities as meaningful, he emphasized that the 25% bar is not relevant to people living with the disease, who generally would view as meaningful any slowing in loss of function. He urged all stakeholders to incorporate the voices of people living with ALS in the design of any future tool designed to measure change/loss of function.

Looking Ahead: Options for Additional/Better Measures in the Future
ROADS & Telemedicine: Dr. Christina Fournier

Dr. Christina Fournier, Emory University (US), presented an overview of two exploratory outcome measures for ALS that are currently being developed and tested in clinical studies for potential future use in evaluation of new therapies. Dr. Fournier emphasized the importance of using these as exploratory endpoints in interventional trials to develop the evidence needed to validate their use for future regulatory review.

The first novel measure, known as ROADS, a pure Patient Reported Outcome (PRO) measure that assesses overall disability level among people living with ALS. In comparison to ALS FRS-R, ROADS targets a broader range of ability levels. ROADS covers 28 tasks, listed in order of difficulty. A one-point change in the ROADS score is a quantifiable measure, and the overall score correlates with survival and the ALS FRS-R, making it clinically relevant. Patients receive the same set of instructions for each item in the survey and the patient is always the rater.

The second measure Dr. Fournier described is called the ALS motor, a telemedicine exam scale that has recently been validated. Since the pandemic, telemedicine has been a mainstay for clinicians to follow their patients. However, there has not been a standardized way to capture data and track progression in a useful manner. A group of experts developed a set of items that assess movements in the bulbar muscles, the neck, the trunk, the arms, and legs, that could be evaluated via a questionnaire conducted using tele-medicine. This tool is being evaluated in the clinical setting (versus a clinical trial) but it has demonstrated a 78% correlation with the ALS FRS-R and an 81% correlation with ROADS.

Looking Ahead: Options for Additional/Better Measures in the Future Addressing Multi-Dimensionality: Dr. Ruben van Eijk

Dr. Ruben van Eijk, University Medical Centre Utrecht (Netherlands), provided a brief overview of issues relating to clinical heterogeneity among patients, including those that are slow progressors and those that have fast progressing ALS. As a result, there is a need to consider ways to consider various levels of importance for items within a composite clinical outcome measure score. All ALS symptoms are not of equal importance to every patient. Dr. van Eijk noted that patient-to-patient heterogeneity means that one person's overall score improvement may not compare to that of another patient as there is no way to tease out which functional area is improving within the composite. Research demonstrates that many patients would not rank the importance of the four ALS FRS-R domains as equal. For example, in the Netherlands, 62% of patients said they would prioritize some domains over others, and the remainder said they had no preference.

To address the limitation of composite scores for outcome measures, Dr. Van Eijk has been working on a statistical weighting approach (Patient Ranked Order Of Function or PROOF) for assessing treatment effect based upon what is important for the patient (as determined by surveys asking what types of outcomes within the ALS FRS-R matter most). PROOF quantifies the patient-level benefit of a drug using a single numerical value that summarizes the improvement in function with the preferences of each individual patient in the study and creates the opportunity to refine risk-benefit assessment of new treatments. The goal of this effort is to develop a composite endpoint for ALS clinical trials that weighs the improvement in symptoms compared to what the patient population wants.

Patients can indicate their ranking of the domains and then those levels of importance scores can be used to prioritize domains that matter most within a clinical trial. Within the trial setting it is possible to conclude that, for the domains that are important for two distinct patients, patient A seems to have a better outcome than patient B. This gives a different outcome than would be reached by looking at the total scores of these patients, in which patient A has a lower total score than patient B. In a randomized trial design, ultimately the "winning probability" is the probability that the patient receiving treatment has a better outcome on domains that are most important to them compared to a patient that is receiving placebo. Dr. van Eijk briefly discussed how to account for a scenario in which a single patient may change their preferences over time as their disease progresses, noting that his team is currently evaluating ways to address this.

Outcome Measures for ALS: Industry Perspective -- Stephanie Fradette

Providing comments from the industry perspective, **Stephanie Fradette** of Biogen, began by reiterating that ALS FRS-R remains an important tool for sponsors of ALS clinical trials with certain benefits, including ease of administration, its correlation with survival, and its acceptability to regulators. She noted that regulators will accept ALS FRS-R but are also keenly focused on survival, especially in Europe and other geographies. She concurred with previous presenters in noting that there are also downsides to ALS FRS-R, including issues with standardization (SOPs) for how it is administered and evaluated, which causes potential issues for trial sponsors that have sites in many locations. Ideally, there would be a more uniform scale that that has been validated with comparable SOPs across the globe. Additionally, sponsors think about the need to enrich their study samples, for example with fast progressing participants to provide confidence that participant cohorts are well balanced at baseline. Given that many people with ALS progress non-linearly, this can be problematic. For example, a

study participant with symptom onset two years ago and slowly progressing disease course until three months before entering the trial would show a slow slope of decline, even though they are progressing very quickly at the time that that they enter on study. She also noted there are multiple attributes that are important to patients and their caregivers that are not measured in the ALS FRS-R, including
mood, frequency of muscle cramping, and twitching fatigue. Finally, she stressed that it would be useful to also evaluate things like weight loss, the ability to stand up from a chair, frequency of falls and other measures that are incorporated in existing ALS PROs.

Group Discussions

Roundtable participants participated in two group discussions to discuss principles for the Alliance and proposed action steps for the community in optimizing clinical trials and outcome measures for ALS/MND.

Each group provided input on a set of principles (a "preamble") for the Alliance on this topic and then offered suggestions for a series of potential community action steps. Key discussion themes to be reflected in the principles included:

- The world is imperfect – we can refine and optimize ALS FRS-R while pursuing development of additional, new measures. Anchor on ALS FRS-R, survival, and QMT.
- It is critically important to engage with people impacted by ALS to understand what is meaningful to them in any effort to refine current outcome measures and develop new ones to measure "clinical meaningfulness."
- There is a need to maintain a global approach to this effort of optimizing clinical trial outcome measures.
- It is necessary to engage all stakeholders, including trial sponsors, regulators, and payers.
- In aiming for greater harmonization and standardization of use and analysis of outcome measures, we need to be able to refine items over time and appropriately reflect language/cultural nuances.
- We need to be aware of potential unintended consequences of efforts to develop new outcome measures for ALS.
- Keep in mind that measures are used both in ongoing clinical care and clinical trials. We must be sensitive to potential impact on the mental health of people living with ALS. Information about measures should be available to people living with ALS, but it is a personal decision about whether they want to focus on their scores.

Proposed action steps included:

- Conduct a landscape assessment/inventory of endpoints being used in ongoing and planned clinical trials.
- Create a Clinical Outcomes Measures Consortium, convened by the Alliance, and led by experts and competent project manager(s), to develop and advance alignment about outcome measures in ALS.
- Advance harmonization among sponsors and investigators for training and evaluation of ALS-FRS-R (consider developing a quality checklist for all sponsors).
- Encourage sponsors to incorporate novel outcome measure approaches (like ROADS, ALS Monitor, PROOF) in their interventional trials and publish the data to build evidence to validate these measures over time.
- Partner with Amylyx to learn from their recent regulatory experience with ALS FRS-R.

- Pursue opportunity for partnership with the US FDA's Critical Path Institute.
- Consider holding an Externally Led Patient Focused Drug Development (EL-PFDD) meeting with FDA (US).

Detailed feedback from the conversations within each group session was combined, resulting in development of the following proposed action plan for the Alliance. Next steps include consideration for adoption by the Alliance in its upcoming meetings and initial activities to implement prioritized action steps.

Alliance Statement & Action Plan [DRAFT]: Optimizing Clinical Trials: Outcome Measures for ALS/MND.

Preamble:

We live in an imperfect world and are dealing with a heterogenous disease that is not well understood.

If we are going to optimize clinical trials, we need to examine outcome measures for ALS/MND.

We can and must improve current outcome measures to evaluate efficacy for new therapies that slow progression of ALS/MND, improve quality of life, and advance survival.

- The perspectives of people living with ALS/MND must be included in any work done on outcome measures.
- We must have a GLOBAL approach to outcome measures.
- All measures must have clinical meaningfulness.

While regulators have approved therapies using ALSFRS – R, an important milestone for our community, we recognize gaps in the current version and seek to collaborate across stakeholders to refine and improve it, including:

- Harmonizing and standardizing approaches for using the instrument and analyzing its measures.
- Enhancing transparency about its use.
- Creating a process for updating and refining the items it evaluates to ensure they are current, relevant to people's daily lives, clear, and easy to interpret.

In parallel to efforts for optimizing ALS FRS-R, we are actively working to develop other validated measures and approaches for teasing out potential benefits that matter to people living with ALS.

- Examples include ROADS, the ALS Monitor (using telemedicine), PROOF
- Trial sponsors should be incorporating these novel endpoints within their trials to help develop evidence needed to validate their use in future registration studies.
- Regulators and payers should be part of the discussion about bringing forward acceptable new endpoints.

In ongoing clinical care and clinical trials, patients should have access to all their health information and be free to choose level of what they want to know and when.

Proposed Action Steps:

Overarching:

- Conduct an inventory of what measures are being used as primary and exploratory endpoints in all ongoing trials
- Create an Outcomes Measures Consortium (work with Critical Path Institute) to include patients, advocates, clinicians, investigators, regulators, and payers.
- Partner with FDA to conduct an EL-PFDD meeting on ALS

ALS FRS-R:

- Designate one entity responsible for ALSFRS-R (e.g., Movement Disorders Society)
- Develop a quality checklist for administering ALS FRS-R
- Harmonize standard operating procedures for ALS FRS-R globally
- Examine feasibility and implications of self-administration of ALS FRS-R
- Revise items in the questionnaire to include current relevant activities and technologies
- Validate translated versions to ensure consistency (e.g., Movement Disorders Translation Cmte)

Future Measures:

- Add novel outcome measures and approaches (ROADS, ALS Monitor, PROOF) into industry trials
- Require inclusion of these novel measures in non-profit organization-funded studies
- Publish data (open source) on novel measures and approaches to validate them (anchor with survival, ALS FRS-R, and QMT)
- Examine Patient Reported Outcome (PRO) measures
- Evaluate what can be measured reliably through telemedicine/ehealth

Sponsors

Thank you to our sponsors for this event; Biogen, Amylyx, Apellis, Mitsubishi Tanabe Pharma, and Cytokinetics. We could've have done it without their support!

Appendix: Selected Presentation Slides

Principles in Design of the Original ALSFRS

- Goals:
  - Develop a simple, 10 -item questionnaire -based scale to record ADL performance.
  - Develop a validated rating scale that would complement QMT and be easy to administer.
  - The scale was to be questionnaire -based and not mix testing modalities (i.e, it should not be a composite scale).
- Models included the Unified Parkinson Disease Rating Scale (UPDRS; Fahn and Elton 1987) and the ALS Severity Scale (ALSSS) developed by Hillel et al (1989).
- Features of the Scale:
  - Each item scored uniformly from 0 (unable to do) to 4 (normal function).
  - Queries patients' CURRENT ability to perform selected ADLs; does not reference past performance.
  - Intermediate scale steps described precisely to try to avoid ambiguity in interpretation.
  - No recall period – the patient is asked about their current ability to perform, not referenced to pre -disease or pre -study baseline.

The Need for Revision and the Birth of the ALSFRS-R

- The original ALSFRS devoted 3 questions to upper extremity, lower extremity and bulbar function, but only one to respiratory function.
- Data from a large multicenter trial of BDNF was used to identify possible additional questionnaire items to be added to the ALSFRS.
  - The Sickness Impact Profile data was also available for comparison
  - Data was also available about patients who began using mechanical ventilation during the course of the study.

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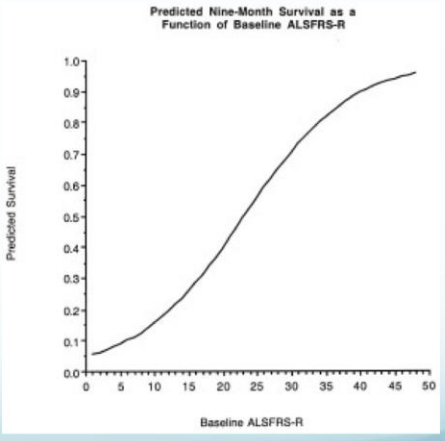
- Data from a large multicenter trial of BDNF was used to identify possible additional questionnaire items to be added to the ALSFRS.
  - The Sickness Impact Profile data was also available for comparison
  - Data was also available about patients who began using mechanical ventilation during the course of the study.

ALSFRS-R Predicts Survival; Scores Represent Clinically Meaningful Changes in Disease Status

- Baseline/entry ALSFRS -R scores have been found to be predictive of survival in clinical trial (Cedarbaum et al 1999); and clinic (Kaufman et al 2005) populations, as has rate of pre-study decline Kimura et al 2006).
- ALSFRS-R scores also predict survival for patients on mechanical ventilation (Lo Coco et al. 2007).
- 93% of 65 clinicians surveyed considered that a 20% slowing in the rate of decline of ALSFRS-R to be a clinically meaningful benefit; and all considered a 25% slowing in the rate of progression to represent a clinically meaningful change (Castrillo-Viguera et al 2010).



ALSFRS-R: The Good, the Bad and the Ugly

Good
Robust – Consistent findings in multiple studies over >20 years
Describes linear disease course in consensus clinical trial populations
Flexible Administration
Reflects Patient Function
Has served as basis of approval for at least 1 drug
Correlates with other measures – Strength, Respiratory, etc and significant disease milestones
Compatible with analysis methods that incorporate death and informative data missingness
Allows uniform assessment of patients in a disorder with variable disease presentations
Predicts survival outcome
Brief

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ALSFRS-R: The Good, the Bad and the Ugly

Bad
Significant interpatient variability
Little data in earliest/latest and/or most/least severe disease stages
Likely floor and ceiling effects for many, if not all individual items and scale domains
Wording of some items not consistent with current practice or use of technologies
Respiratory Domain correlates poorly with the other domains
Ordering of responses for many items is poor according to Rasch analysis
Combines several domains into a single outcome, which may hide interpatient differences

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ALSFRS-R: The Good, the Bad and the Ugly

Ugly
Many item response choices are difficult for patients to differentiate
Does not incorporate domains of patient experience that we now recognize as important, such as cognition, mood and pain
No complete, standardized administration manual
No recognized, authoritative group taking ownership and responsible for oversight of scale use

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Challenges for the Future

- Need for standardization
  - Linguistic
  - Cultural
  - Administration and Training Standards
- Further determination of magnitude of change that represents a clinically meaningful benefit
- Potential for modifications/additions
  - Finer grading, especially for earliest manifestations of dysfunction
  - Evaluation of impairment in additional domains: cognition, pain, others
  - Assembly into composite measure with functional test battery
  - Updating to reflect modern technology and technology usage
  - Involvement of patients and caregivers to improve the relevance and understandability of questions

ALS Regulatory Guidance: Primary and Secondary Endpoints

FDA Guidance (September 2019)

Sponsors should characterize an effect on mortality in all ALS development programs because it is important to the consideration of the overall safety and effectiveness profiles. If patient function is intended to be assessed by the primary outcome, mortality should be integrated into the primary outcome by an analysis method that combines survival and function into a single overall measure, such as the joint rank test (see section III.B.4.b., Integrated assessment of function and survival). In that situation, the independent assessment of a drug effect on survival should be a secondary endpoint. The independent assessment of survival should be combined with an evaluation of the need for full-time (or nearly full-time) respiratory support because such support can affect survival time. Survival is also acceptable as a primary outcome measure.

- Section II.2.B: Effectiveness Endpoints
  - If patient function is used as the primary outcome:
    - Mortality should be integrated into the primary outcome by a combination measure (i.e. joint rank test combining survival and function)
    - Independent assessment of survival as a secondary endpoint

      Independent assessment of survival should be combined with an evaluation of the need for full-time (or nearly full-time) respiratory support
  - Survival is also acceptable as a primary outcome measure

neuro

EMA Guidance (November 2015)

Efficacy endpoints and methodological considerations

A response criterion that could be considered a clinically meaningful outcome in clinical trials should be defined and justified a priori. In general endpoints from the domains of disability and survival should be pre-specified to estimate slowing of disease progression and increased survival. As primary efficacy variable in ALS trials can use either time to death including other end of life measures that prolong life in ALS patients (e.g. non-invasive ventilation [NIV], ventilation via tracheostomy) or function (ALSFRS-R) (see section 6), or both. For proof of efficacy a clear and significant effect on one domain and a trend on the other may be sufficient. The choice of primary endpoint should not lead to insufficient data for assessing the effect on survival.

Alternatively, other primary endpoints might be considered such as a time-to-event endpoint with the event defined as death or a predefined deterioration on the ALSFRS-R scale or a composite endpoint of survival and functioning (Finkelstein 1999; Berry 2013; Cudkowicz 2013). In this case the overall results should not be driven by a change in one or the other but on both.

- Section 8.2.1: Trials for disease modifying treatments
  - Primary efficacy endpoint can use either:
    1) time to death including other end of life measures OR
    2) function (i.e. ALSFRS-R) OR
    3) both
       - For proof of efficacy a clear and significant effect on one domain and a trend on the other may be sufficient
  - Alternatively, other primary endpoints such as a time-to-event endpoint with the event defined as:
    1) death OR
    2) a predefined ↓ALSFRS-R OR
    3) a composite of survival and functioning
       - In this case, the overall results should not be driven by a change in one or the other but on both

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EMA Regulatory Guidanceon Symptomatic Therapies

8.2.2. Trials for symptomatic treatments and related function

For treatments whose mechanisms of action are expected to improve symptoms of ALS but would not have a beneficial effect onisease progression, trials should aim to demonstrate a beneficial effect on both symptoms (muscle strength) and functioningSuitable candidates for development as symptomatic treatments could potentially include products with a direct action on muscles or an effect on neuronal conduction that does not affect the neurodegenerative process and would be expected to be reversible on cessation of treatmen Effect on disease progression should still be measured however to exclude a negative effect of treatment. Non-specific symptomatic treatments, for example anti-spasticity drugs, would generally not be approvable for a "pseudospecific" indication for symptomatic treatment ofALS.

Study duration

Study duration for medicinal products with an effect only on symptomatic improvement (e.g. muscle strength and related functin) may in principle be of shorter duration than for products with potential diseasemodifying effects. Depending of the mechanism of action, pivotal efficacy trials of 3 to 6 months duration could be sufficient Safety data over 12 months are required to exclude negative impact on disease modifying outcomes (e.g. survival as a key safety outcome).

Efficacy endpoints

For products developed for symptomatic treatment, muscle strength and function are considered the most important endpoints and should show consistency in effects According to the expected effect, one should be selected as primary endpoint and the other as secondary endpoint. However, this only holds true for products that by their mechanism of action do not affect the neurodegenerative process and it will be necessary to estimate the extent of the possible adverse effects on disease progression and survival and to discuss this in relation to the clinical relevance of the results.

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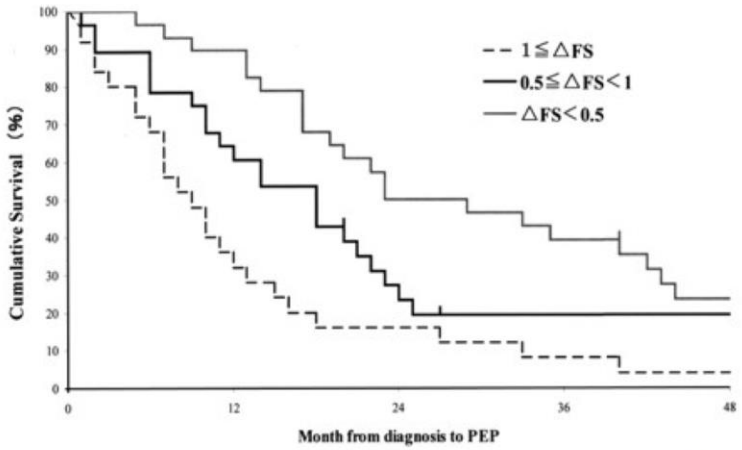
ALS Function Rating Scale - Revised

- **ALS F**unctional **R**ating **S**cale – **R**evised
- Change in functional status from symptom onset
  - *Patient's perception of how they are doing
- Evaluates 4 levels of function:

Progression rate of ALSFRS -R at diagnosis has been shown to correlate with survival



Kimura et al. 2006

Limitations

- Subjective scale – sometimes need prompting when there is a contraindication between patient report and observable data
- Does not take in to account any changes in cognitive behavior – function can change due to this
- Best to have team discuss how the tool with be used. In a review of our clinic functioning, it was noted that during clinic visits patients and families felt there was "+++" repetition
- If each specialist is scoring, there can be up to 3-4 professionals rating. It's not clear if that is how the tool was intended to be used
- Patient self-rating can be unrealiable.
  - Our experience: administering the ALSFRS -R over the phone can also be challenging
- Some patients find this conversation, around "sum of losses" to be difficult.

Best practices in implementation

- In order to obtain the most consistent and accurate results, it is best to have 1-2 key individuals administering the tool
  - Should have discussions to ensure their interpretation of rating is the same (inter-rater reliability)
- Best to administer the tool at each clinic visit
- Typically do not share the score with the patients. Quantitative loss of function can be devastating
  - Patients don't ask/don't track themselves as they often do with FVC/SVC
- Personal experience & opinion: in-person assessment results in more accurate results than over the phone or self-administered.

Qualitative Evaluation of the ALSFRS-R Survey

Methods

- Web-based survey
- 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?"

Results

- 57 participants (72% participants with ALS, 28% caregivers) responded to at least one item question
- 41 participants expressed concern about at least one item.

Results

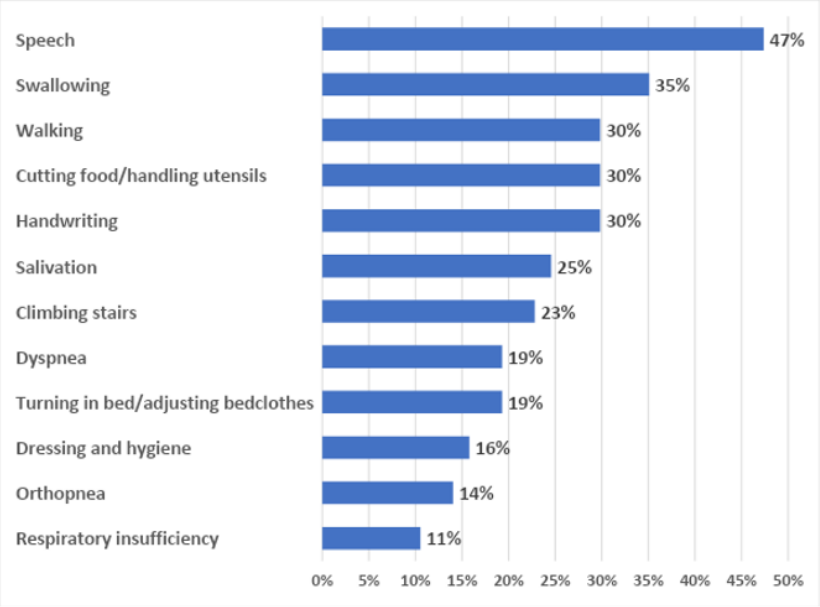
Two categories

- Criticisms that could be addressed in a manual/instructions
- Issues with the items/responses that would require measure modification

Common criticisms

- Language used is of a medical literacy level too high
- Response to item is situational - time of day, use of equipment
- Difficult to distinguish the difference between response choices
- The structure and/or underlying assumptions of the item makes it difficult to answer.

Percent of critiques by domain 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?'(n=57)



ROADS: Overview

- The ROADS is a patient-reported outcome measure that assesses overall disability level in people with ALS
- 28 items, each scored 0, 1, or 2

Task		Unable to perform [0]	Abnormal: able to perform but with difficulty [1]	Normal: able to perform without difficulty [2]
1	nod yes or no?	[ ]	[ ]	[ ]
2	ride in a car?	[ ]	[ ]	[ ]
3	eat soup?	[ ]	[ ]	[ ]
4	drink milkshake or smoothie?	[ ]	[ ]	[ ]
5	sit on a toilet?			
6	swallow pills?			
7	blow out a candle?			
8	eat dry food(e.g. cornbread)?			
9	speak on the phone?			
10	drink out of a glass?			
11	eat a large meal?			
12	sign name on paper?			
13	get into bed?			
14	roll over in bed?			
15	take a shower?	[ ]	[ ]	[ ]
16	use a knife and fork?	[ ]	[ ]	[ ]
17	walk around your home?	[ ]	[ ]	[ ]
18	move a chair?	[ ]	[ ]	[ ]
19	speak in a loud room?	[ ]	[ ]	[ ]
20	speak for hours?	[ ]	[ ]	[ ]
21	clip nails?	[ ]	[ ]	[ ]
22	walk up 1 flight of stairs?	[ ]	[ ]	[ ]
23	walk up a hill?	[ ]	[ ]	[ ]
24	climb a stepstool?	[ ]	[ ]	[ ]
25	get up from the floor?	[ ]	[ ]	[ ]
26	carry an object going downstairs?	[ ]	[ ]	[ ]
27	stand for hours?	[ ]	[ ]	[ ]
28	get heavy objects off a high shelf?	[ ]	[ ]	[ ]

ROADS Summary

- The ROADS is a simple, Rasch-built, patient-reported outcome measure to quantify overall disability status in ALS
- Linearly-weighted (one point is a quantifiable measure)
- Improved item targeting to wider range of difficulty levels compared to ALSFRS-R
- High test-retest reliability
- Clinically meaningful and predictive of survival

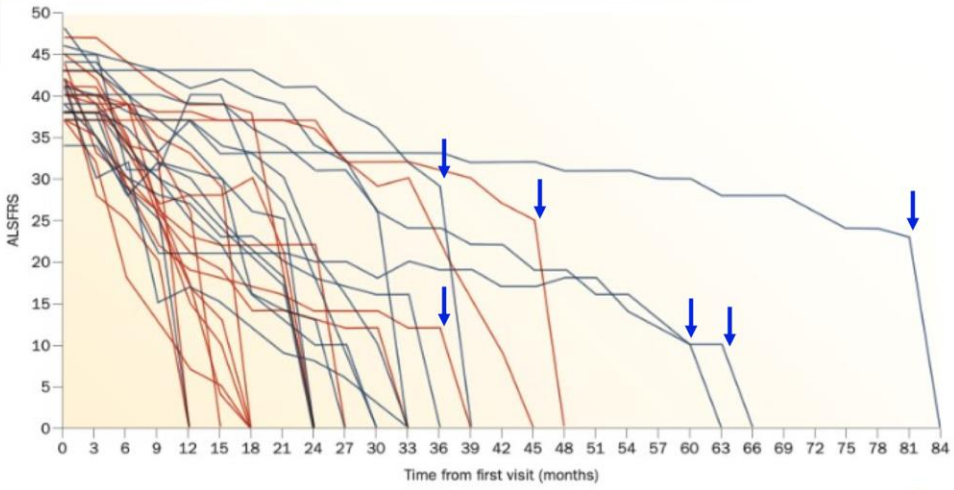
ALS MOTOR: methods

- Draft scale with 25 items assessing movement in the bulbar muscles, neck, trunk, and extremities was created by an ALS expert panel, incorporating input from PALS advisors
- Administered to 258 PALS representing the full spectrum of a typical ALS clinic population
- Rasch analyses performed: 3 items were removed, and item response categories were consolidated for 8 items

ALS MOTOR: Reliability and Validity

- Inter-rater reliability = 98%
- ALS MOTOR has 78% correlation with ALSFRS-R
- ALS MOTOR has 81% correlation with ROADS

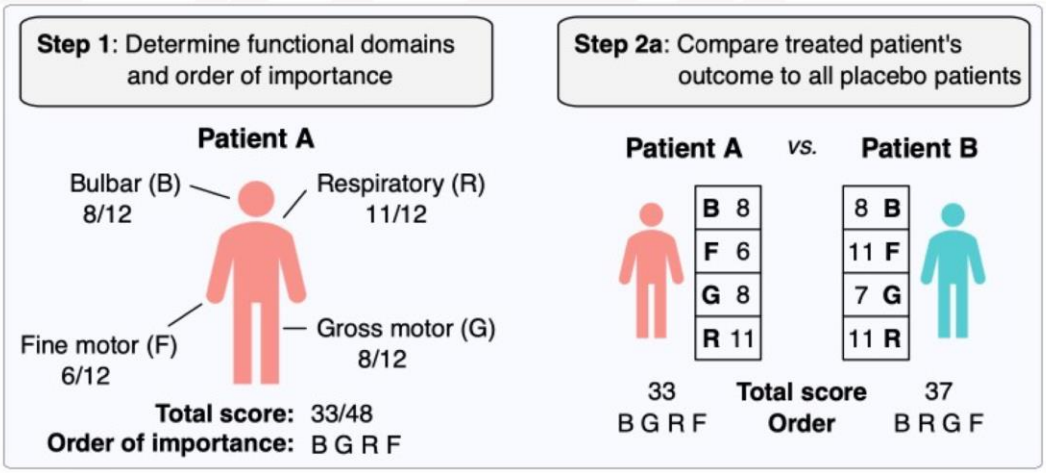
Are all symptoms of equal importance?



Swinnen B & Robberecht W.
The phenotypic variability of amyotrophic lateral sclerosis Nat Rev Neurol 2014

TRICALS

Patient-Ranked Order of Function (PROOF)



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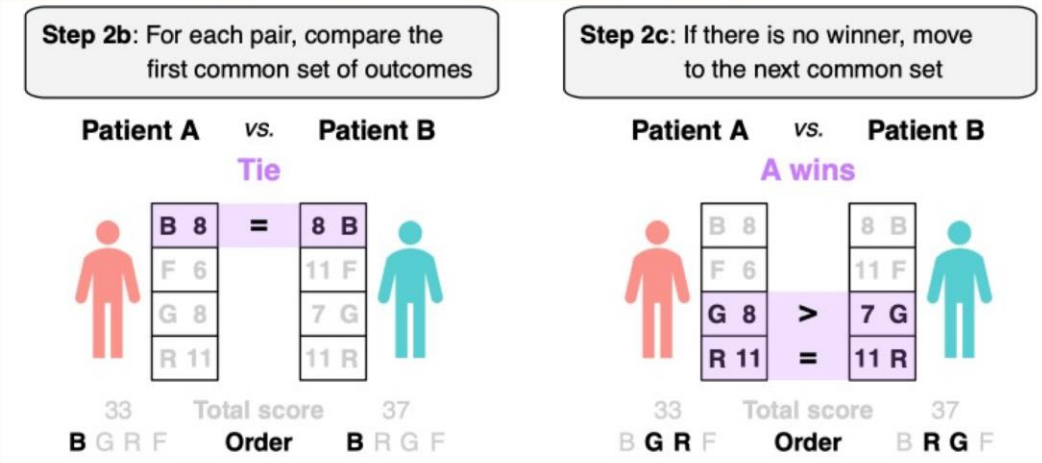

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