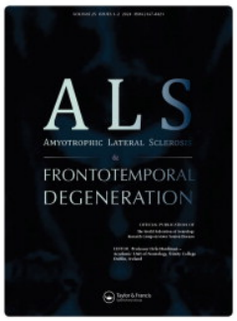

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Harmonized standard operating procedures for administering the ALS functional rating scale-revised

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RESEARCH ARTICLE

Harmonized standard operating procedures for administering the ALS functional rating scale-revised

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Abstract

The ALS Functional Rating Scale-Revised is the most commonly used primary outcome measure in current ALS clinical trials. While rigorous training and certification is generally recognized as critical to reliable performance, differences have existed between training in the two groups responsible for most training in ALS outcome measures. We present a harmonized standard operating procedure which is intended to further reduce response variability by the use of identical training in North America and Europe.

Keywords: *Clinical trial, ALSFRS-R, training*

The ALS Functional Rating Scale was introduced as an outcome measure for ALS trials in 1996, when it was used as a secondary outcome measure in a clinical trial of CNTF in patients with ALS (1). The original scale was a 10 item instrument assessing bulbar function, fine motor function, gross motor function, and respiratory symptoms. Respiratory function was assessed in only a single question, and the scale was revised to include 2 additional respiratory questions, which was used as a secondary measure in a trial of BDNF (2). It has been extensively investigated subsequently, and found to predict clinically relevant outcomes such as survival and pulmonary function, show excellent reproducibility, and be equivalent whether obtained in person or by telephone. Since 1996, the ALSFRS or ALSFRS-R has been used in 38 clinical trials enrolling more than 100 participants, including 19 as the primary outcome measure (3).

The ALSFRS and ALSFRS-R were designed to be administered using a structured interview, during which the evaluator probes the participant responses, both to verify responses and accurately place the participant status within a 5 point scale. Because of this interactive method of administration, training evaluators to perform this assessment is critical both for reproducibility within and across participants. Over the last 20 years, this training has been designed and implemented by two main groups: the Northeast ALS Clinical Trials Consortium (NEALS) in collaboration with individuals at Upstate Medical University in Syracuse and later at the Barrow Neurological Institute in Phoenix, and ENCALS/TRICALS coordinated by individuals at UMC Utrecht, the Netherlands.

The NEALS consortium first conducted standard training and certification of performance in conjunction with a trial of topiramate in ALS (4). This was followed by NEALS administered trials of celecoxib, lithium, ceftriaxone, creatine and PB/Turso (5–9). The same training group has also performed training and certification activities for the ALSFRS-R and other outcome measures for industry sponsored trials of dexpramepexole, tirasemtiv, azanezumab, reldesemtiv, NP001, and tofersen (10–17). During this time frame, study specific training manuals and standard operating procedures were generated which varied slightly in

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detail, but which have remained very consistent in the previous 5 years.

Since 2016, ENCALS/TRICALS have also trained and certified assessors in the administration of the ALSFRS at the annual ENCALS/TRICALS meetings. This was done in parallel with the training and certification of the careful performance of other outcome measures used in clinical trials, such as vital capacity, dynamometry, Edinburgh Cognitive Assessment Scale (ECAS) and King's staging. Training and certification were conducted in investigator-initiated studies, such as TUDCA, lithium (on UNC13a risk genotypes), and Triumeq, as well as industry-sponsored studies, such as ORARIALS, RT001, PHOENIX, DAZALS and ADORE (e.g. (12,18–20)). The ENCALS/TRICALS training was based on the standard operating procedure (SOP) developed in 2015. The initial training consists of a face-to-face training with a video score exam. Since 2017, an online training platform has been included as part of the training process to be able to provide (an update of) training more often.

While the NEALS and ENCALS/TRICALS training instruction and certification process are similar, important differences have been noted that have the potential to alter scoring. Several examples are presented here. In item 1, the ENCALS/TRICALS SOP mandates a specific score if a participant requires repetition for speech to be understood 25% of the time; the NEALS SOP assigns this score if repetition is required on a daily basis. For item 2, a specific score for salivation requires the participant reporting that they use a tissue to dab their mouth 25% of the time or more, while the NEALS SOP has no numeric criterion. Item 10 asks about dyspnea, or shortness of breath; the ENCALS/TRICALS scoring mandates the lowest possible score if noninvasive ventilation is used at all, while the NEALS SOP instructs the evaluator to score this item according to how a participant feels when noninvasive ventilation is not being used. Each of these items would be potentially scored differently depending on these instructions. Scoring for other questions also have differences, but are minor compared to the differences of the examples noted above. Table 1 shows all prior differences between the ENCALS/TRICALS SOP and the NEALS SOP, with the final harmonized wording also shown.

Given the multinational character of many current and planned clinical trials, and the fact that a single evaluator is very likely to receive training both according the NEALS and the ENCALS/TRICALS SOPs, the developers and trainers from the two groups felt it was imperative to train evaluators in a consistent manner. For this reason, meetings were held during the summer of 2022 to harmonize training and certification practices. As the ALSFRS-R remains the most commonly employed primary outcome measure for ALS trials, we believe that it is critical that this harmonized set of instructions be available to the ALS community and present them here. We hope that this SOP will be adopted universally; this will improve consistency and reliability of administration of a tool that remains the mainstay of ALS clinical trials.

ALS Functional Rating Scale Revised (ALSFRS-R) Standard Operating Procedure (SOP)

This SOP is designed to help standardize the administration of the ALSFRS-R

The ALSFRS-R is a scale designed to assess daily function as rated by the participant with the assistance of a trained evaluator. The questions should be asked broadly; based on the response, the evaluator should probe to validate the response and help the participant determine which of the choices for each question are most appropriate. The goal of the evaluator is to help the participant determine accurately their level of function, not to push the response to either a higher or lower score. If the scale is administered over the telephone and the participant is unable to respond because of significant bulbar impairment, a caregiver should relay the questions and responses without interpretation. The participant should be able to hear the questions directly, so use of speaker phone is preferred.

As a general rule, "help" means help from a caregiver or a device or appliance. For example, use of a handrail, ankle foot orthosis (AFO) or walking stick would count as help with walking.

For each question, responses should be recorded according to the closest level within each 5 point list, in which 4 reflects normal function or no change from prior to onset of any symptoms of ALS, and 0 reflects no function.

Occasionally, participants provide responses clearly at odds with the observed function of the participant. In such cases, clarification can be asked; for example "You report normal speech but I am hearing significant slurring." In most cases, the participant will modify their responses; however if the participant persists in their report of function, their assessment must be recorded.

Some questions may ask about functions that are no longer being performed, even though the participant thinks they might be able to do so. In such situations the rater should score according to what is being performed, not what hypothetically could be performed. In cases of temporary disability (such as a cast on an arm) the evaluator should rate according to what the patient is able to do at the current time.

The same evaluator should perform the evaluation on a given patient throughout the course of a study.

Table 1.. Summary of changes: NEALS, TRICALS and harmonized ALSFRS-R guidance.

	NEALS ALSFRS-R Guidance For Scoring Level	TRICALS ALSFRS-R Guidance For Scoring Level	Harmonized ALSFRS-R Guidance For Scoring Level
1. Speech	2 - Some repetition required to understand speech in daily conversations	2 - "Intelligible with repeating" means that >25% of the time, repeating is necessary for comprehension.	2 - Significant repetition is required for normal conversation.
2. Salivation	3 - Swallowing more frequently. 2 - Occasionally dabbing at at the mouth with a tissue.	3 - "Slight saliva" with or without night time drooling, means that there is an excess, but there is usually no need to mop up the saliva with a tissue. 2 - "Moderately excessive saliva" means that a tissue needs to be used, but <25% of the time.	3 - Some excess saliva, but no need to mop up. 2 - Reports occasionally dabbing the mouth with a tissue during the day.
3. Swallowing	3 - Careful with foods because they get caught in throat; can eat all foods of choice but with occasional choking. 2 - Avoids certain foods or requires that consistency of foods be changed. 1 - Needs to have a gastrostomy to rate as 1.	3 - "Early eating problems" means that occasionally food will stick, or cause coughing or choking. Food may need to be cut up small, but is not mashed or liquidized. 2 - "Dietary consistency changes" means that food needs to be mashed or liquidized, drinks may need thickener, or some foods such as steak, dry biscuits or cornflakes are avoided in favor of yoghurts, casseroles or porridge. 1 -"Needs supplemental tube feeding" means that oral intake of food is so difficult that significant weight loss (>10%) has occurred and gastrostomy is required to supplement caloric intake *regardless of whether one is fitted or not*.	3 - There are early eating problems; occasionally food may stick in the mouth or throat, or cause coughing or choking. 2 - Dietary consistency changes are required. Dietary consistency changes are defined as: Food needs to be mashed, liquidized, or cut into smaller pieces to allow swallowing, drinks need thickener, or some foods are avoided in favor of others that are easier to swallow. 1 - The participant cannot maintain weight by oral intake due to swallowing issues, whether or not a feeding tube is in place.
4. Handwriting	Consistent guidance		No change
5a. Cutting food and handling utensils	3 - Some difficulty cutting or handling utensils by methods used prior to disease onset but continues to do so independently. Does not use altered utensils. 2 - If assistance is required, but still tries to cut some foods, and still does >50% of the task successfully. Adaptive utensils/tableware is rated as 2. 1 - Cannot cut foods by methods used prior to disease onset, but still tries to feed themselves and succeed at least occasionally.	3 -"Somewhat slow and clumsy, but no help needed" means that there is some difficulty either cutting food or holding utensils, but the patient is able to do this independently. Use of large handled cutlery to achieve the task counts as slow and clumsy. 2-"Can cut most foods although slow and clumsy; some help needed" means that occasionally assistance is needed, but the patient is independent for the task otherwise. 1 - Assistance is needed at least half the time for cutting but not for feeding. 1-"Food must be cut by someone but can still feed slowly" means that assistance is required at least half the time for cutting but not for feeding. For example, if food must be cut	3 - There is some difficulty either cutting food or holding utensils, but the participant is able to do this independently. 2- If occasional assistance is needed for cutting food, but the participant is independent for the task otherwise. Use of altered utensils constitutes assistance and is rated 2. 1 - Assistance is required at least half the time for cutting but not for feeding.

(*Continued*)

Table 1.. (*Continued*).

	NEALS ALSFRS-R Guidance For Scoring Level	TRICALS ALSFRS-R Guidance For Scoring Level	Harmonized ALSFRS-R Guidance For Scoring Level
		but the patient can feed themselves otherwise, score 1.	
5b. CUTTING FOOD AND HANDLING UTENSILS:	Consistent guidance		No change
6. Dressing and hygiene	2 - Methods used now are different than those used prior to disease onset. Substitute methods can include: sitting to get dressed, use of shower chair, sitting on a stool to shave and/or brush teeth, using built up toothbrush, Velcro clothes, pull-on clothes, adaptive clothes, not wearing pants anymore because skirts are easier. Caregiver assistance is not required. 1 - Needs daily caregiver for assistance with dressing but patient has some level of function.	2 - "Intermittent assistance or substitute methods" means that some help is needed either from a caregiver or by use of devices such as button hooks or self-tying laces, but the patient is otherwise independent. If the patient has changed the clothing they normally wear such as having zipped clothing instead of buttons, score as substitute method. 1 -"Needs attendant for self-care" means that all aspects of the task require assistance, but the patient is able to assist the caregiver for much of it	2 - Methods used now are different than those used prior to disease onset. Minimal help is needed either from a caregiver or by use of devices such as button hooks or self-tying laces, or clothing used has changed for reasons of ease of use, but the participant is otherwise independent. 1 - Both dressing and hygiene activities require significant level of caregiver assistance, but the participant is able to assist the caregiver.
7. Turning and adjusting bedclothes	Consistent guidance		No change
8. Walking	Consistent guidance		No change
9. Climbing stairs	Consistent guidance		No change
10. Dyspnea	If a participant is using noninvasive ventilation (NIV), score according to when NIV is not being used.	If someone is using noninvasive ventilation at night or in the day for ALS, score 0.	If a participant is using noninvasive ventilation (NIV), score according to when NIV is not being used.
11. Orthopnea	Rate 0 if using nocturnal BiPAP and patient NEVER sleeps without device. If patient uses BiPAP, but sometimes sleeps without it, select the number that best describes the patient's orthopnea when sleeping without device 3 –I f a patient can sleep flat on their side but has avoided sleeping on their back since symptom onset, rate as 3 0 - If patient is using NIV at night and cannot sleep without it	Score based on difficulty regardless of the apparent underlying cause (so for example, needing to sleep sitting up because of excessive saliva scores 1). Treat a hospital style bed in which the back can be raised independently as if pillows were in place of the raised section. 3 - If there is difficulty falling asleep or if the patient wakes because of breathlessness but they do not use more than two pillows, score 3. 0 - If noninvasive ventilation is used most or all of the night, score 0. If NIV is used for an hour or so only, score as if not used.	Score based on difficulty regardless of the apparent underlying cause (for example, needing to sleep sitting up because of excessive saliva scores 1). Treat a hospital style bed in which the back can be raised independently as if pillows were in place of the raised section. 3 - if there is difficulty falling asleep, or if the participant wakes because of breathlessness but they do not use more than two pillows, or if they have changed their sleeping position (i.e. from supine to the side, prone to side, etc.). 0 - If using nocturnal BiPAP or any form of NIV and the participant NEVER sleeps without device. If the participant uses BiPAP or other form of NIV, but sometimes sleeps without it, select the number that best describes the participant's orthopnea when sleeping without device.
12. Respiratory insufficiency	Consistent guidance		No change

Evaluator training and certification is essential to the successful use of this questionnaire. Annual refresher training is required to maintain certification. Training should be conducted by experts in ALS clinical assessment associated with major clinical trial networks.

Item 1: SPEECH

Ask "How is your speech?" The participant is to compare his/her current function with function prior to any symptoms of ALS.

Rate 4, if the participant notes completely normal speech (speech as it was prior to onset of ALS symptoms).

Rate 3, if there is any change in speech including softer speech/reduced volume.

Rate 2, if the participant feels that significant repetition is required for normal conversation. Rate 1, if gestures or communication aids are required to understand speech. Speech amplification devices and/or a soft palate prosthesis are considered communication aids and their use would mandate a rating of 1.

Rate 0, if impossible for the participant to communicate verbally.

Item 2: SALIVATION

Ask "How is your saliva?" Rate the participant's current status versus prior to ALS onset regardless of whether the participant is taking medication for salivation. Any saliva removal with a cloth, wipe, or hand is considered a 2 or less.

Rate 4, if there is no excess saliva. Some participants may report a dry mouth; however if saliva is never in excess the rating remains 4.

Rate 3, if the participant experiences some excess saliva, but there is usually no need to mop up the saliva with a tissue, or if there is new nighttime drooling.

Rate 2, if the participant reports occasionally dabbing the mouth with a tissue during the day.

Rate 1, if drooling occurs and a tissue is used often, but not continuously.

Rate 0, if constant use of tissue or handkerchief or suction is required.

Item 3: SWALLOWING

Ask "How is your swallowing?"

Rate 4, if there is no change in chewing or swallowing from prior to onset of ALS symptoms; the participant should be able to eat any food in typical mouthful sizes or drink liquid without difficulty.

Rate 3, if there are early eating problems; occasionally food may stick in the mouth or throat, or cause coughing or choking.

Rate 2, if dietary consistency changes are required. Dietary consistency changes are defined as: Food needs to be mashed, liquidized, or cut into smaller pieces to allow swallowing, drinks need thickener, or some foods are avoided in favor of others that are easier to swallow.

Rate 1, if the participant cannot maintain weight by oral intake due to swallowing issues, whether or not a feeding tube is in place.

Rate 0, if the participant reports no oral intake (NPO). This status requires parental or enteral feeding. NPO means they are not swallowing anything (not even sips of coffee or other drinks; if they do so for reasons of taste, it must be suctioned or spit out).

Item 4: HANDWRITING

Ask ''How are you writing using your dominant hand?'' Rate without use of any assistive devices, such as foam tubing &/or mechanical aids due to finger weakness. If such devices are used routinely, ask how writing is without their use. If participant is unsure, either ask them to demonstrate, or rate as 0. Handwriting refers to either printing or cursive; however, if there has been a switch from one to the other, grade as 3 or less.

Rate 4, if there is no change from prior to onset of ALS symptoms.

Rate 3, if all words are legible, while using a normal pen, but there is a change in writing.

Rate 2, if some words cannot be read but others can.

Rate 1, if the participant can only write their name or sign, but other writing is illegible. If the participant has not written other words except their name or signature recently and therefore cannot answer the question further, score as 1.

Rate 0, if the participant cannot hold a pen in a normal writing position.

Item 5a: CUTTING FOOD AND HANDLING UTENSILS (patients without gastrostomy)

Ask "How are you with cutting food or handling utensils?" If a participant has a gastrostomy but it is not the primary method of caloric intake, treat as "without gastrostomy".

Rate 4, if there is no change from prior to onset of ALS symptoms, and there has been no change in the type of utensil used (for example chopsticks to knife and fork, or tendency to use a spoon now).

Rate 3, if there is some difficulty either cutting food or holding utensils, but the participant is able to do this independently.

Rate 2, if occasional assistance is needed for cutting food, but the participant is independent for the task otherwise. Use of altered utensils constitutes assistance and is rated 2.

Rate 1, if assistance is required at least half the time for cutting but not for feeding. For example, if food must be cut but the participant can feed themselves otherwise, rate as 1.

If the participant cannot cut foods but still try to feed themselves and succeed at least occasionally, rate as 1.

Rate 0, if assistance is needed for all aspects of feeding. If a participant chooses not feed themselves for any reason rate as 0. If a participant feeds themselves without the use of their arms, rate as 0.

Item 5b: CUTTING FOOD AND HANDLING UTENSILS (alternate scale for patients with gastrostomy)

Ask "How are you with handling the gastrostomy fastenings and fixtures?" If someone has a gastrostomy and it is the primary method of caloric intake, treat as "with gastrostomy". "Normal" means that there is no difficulty at all with any manipulations.

Item 6: DRESSING AND HYGIENE

Ask "How are you with dressing and washing?"

Rate 4, if there is no change compared with before symptom onset.

Rate 3, if the participant is slower than before but remains independent, and does not use any assistance, has not changed the types of clothing worn to make dressing easier, and is not using different methods.

Rate 2, if methods used now are different than those used prior to disease onset. Minimal help is needed either from a caregiver or by use of devices such as button hooks or self-tying laces, or clothing used has changed for reasons of ease of use, but the participant is otherwise independent.

Rate 1, if both dressing and hygiene activities require significant level of caregiver assistance, but the participant is able to assist the caregiver.

Rate 0, if the participant is completely unable to carry out any aspect of these activities and cannot significantly help the caregiver. If someone decides not to dress or bathe themselves but would otherwise be able to, score 0.

Item 7: TURNING IN BED AND ADJUSTING BED CLOTHES

Ask "Can you turn in bed and adjust the bed clothes?"

Rate 4, if there is no change from prior to onset of ALS symptoms.

Rate 3, if there is difficulty with either or both, but both activities are completed independently.

Rate 2, if a participant can complete one task independently but not the other.

Rate 1, if both the process of turning and adjusting bedclothes cannot be completed without assistance.

Rate 0, if the participant cannot or chooses not to turn in bed or adjust bed clothes for whatever reason.

Item 8: WALKING

Ask "How is your walking?" This question refers to walking ability as it relates to change in leg function. Do not rate according to shortness of breath.

Rate 4, if there is no change from prior to onset of ALS symptoms with walking ability as related to normal daily activities.

Rate 3, if there is some difficulty walking which might include slowing, tripping or imbalance, but no assistance is routinely needed either in the form of help from someone else, or by the use of an AFO, a walking stick, or frame/walker.

Rate 2, if assistance from a physical aid (including AFO, walking stick or frame/walker) or caregiver is needed.

Rate 1, if the participant can help with transfers by weight bearing but cannot ambulate.

Rate 0, if the participant cannot stand and bear weight.

Item 9: CLIMBING STAIRS

Ask "Are you able to climb stairs?" Only rate ability for walking up stairs, not down. Stairs must include 3 steps to be evaluated.

Rate 4, if there is no change from prior to onset of ALS symptoms with climbing stairs, including use of a hand rail.

Rate 3, if there is some slowing compared to baseline but the participant does not rest between steps or feel unsteady.

Rate 2, if the participant does need to rest or feels unsteady.

Rate 1, if use of a handrail or help from a caregiver is required to climb stairs.

Rate 0, if a participant cannot climb stairs or does not climb stairs for any reason score 0.

Item 10: DYSPNEA

Ask ''Are you experiencing shortness of breath?'' *If a participant is using noninvasive ventilation (NIV), score according to when NIV is not being used. Use the term shortness of breath (SOB) rather than dyspnea.*

Rate 4, if SOB does not occur more frequently or with different activities than prior to ALS symptom onset.

Rate 3, if SOB occurs with walking. Walking is defined as a comfortable speed on a flat surface.

Rate 2, if SOB with talking or any other daily activity besides walking; SOB with activities not specifically listed in the question is nonetheless rated as 2.

Rate 1, if SOB is present at rest.

Rate 0, if SOB is continuous and uncomfortable rate as 0 regardless of whether assisted ventilation is used. Continuous use of ventilation is defined as use for more than 22 hours daily for 7 consecutive days. Under these circumstances, rate as 0.

Item 11: ORTHOPNEA

Ask "Can you sleep lying down flat or do you need to be propped up?" Score based on difficulty regardless of the apparent underlying cause (for example, needing to sleep sitting up because of excessive saliva scores 1). Treat a hospital style bed in which the back can be raised independently as if pillows were in place of the raised section.

Rate 4, if sleep position has not changed from prior to onset of ALS symptoms.

Rate 3, if there is difficulty falling asleep, or if the participant wakes because of breathlessness but they do not use more than two pillows, or if they have changed their sleeping position (i.e. from supine to the side, prone to side, etc.).

Rate 2, if more than two pillows are needed.

Rate 1, if the participant sleeps sitting up in bed or in a chair.

Rate 0, if using nocturnal BiPAP or any form of NIV and the participant NEVER sleeps without device. If the participant uses BiPAP or other form of NIV, but sometimes sleeps without it, select the number that best describes the participant's orthopnea when sleeping without device.

Item 12: RESPIRATORY INSUFFICIENCY

Ask:"Do you use noninvasive ventilation?" This question refers to any sort of noninvasive technique, including CPAP but excluding cough assist devices. Any use of NIV for any reason is rated at most 3.

Rate 4, if the participant does not use noninvasive ventilation.

Rate 3, if Intermittent use during the day or night.

Rate 2, if intermittent use during the day and continuous at night.

Rate 1, if using NIV continuously, during night and day, defined as more than 22 hours per day for 7 consecutive days.

Declaration of interest

JM Shefner: has received personal compensation from: Amylyx; Cytokinetics; Denali; GSK; Mitsubishi Tanabe Pharma America; Neurosense; Orthogonal; RRD; Acurastem; Revalasio; Apellis; Swanbio; Novartis; Sanofi. He has received research funding from: AB Sciences; Acorda Therapeutics; Alector; Amylyx; Biogen; Cytokinetics Incorporated; Ionis; Mitsubishi Tanabe Pharma America; Quralis; PTC; Sanofi; Wave; Myolex.

T Bunte: has nothing to declare.

G Kittle: has nothing to declare.

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