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Amyotrophic Lateral Sclerosis Clinical Trials and Interpretation of Functional End Points and Fluid Biomarkers
A Review

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IMPORTANCE Clinical trial activity in amyotrophic lateral sclerosis (ALS) is dramatically increasing; as a result, trial modifications have been introduced to improve efficiency, outcome measures have been reassessed, and considerable discussion about the level of data necessary to advance a drug to approval has occurred. This review discusses what recent pivotal studies can teach the community about these topics.

OBSERVATIONS By restricting inclusion and exclusion criteria, recent trials have enrolled populations distinct from previous studies. This has led to efficacy signals being observed in studies that are smaller and shorter than was thought feasible previously. However, such trials raise questions about generalizability of results. Small trials with equivocal clinical results also raise questions about the data necessary to lead to regulatory approval. The ALS Functional Rating Scale–Revised remains the most commonly used primary outcome measure; this review discusses innovations in its use. Blood neurofilament levels can predict prognosis in ALS and may be a sensitive indicator of biologic effect; current knowledge does not yet support its use as a primary outcome.

CONCLUSIONS AND RELEVANCE It is now possible to use specific inclusion criteria to recruit a homogeneous patient population progressing at a specific rate; this will likely impact trials in the future. Generalizability of results on limited populations remains a concern. Although clinical outcomes remain the most appropriate primary outcome measures, fluid markers reflecting biologically important processes will assume more importance as more is learned about the association between such markers and clinical end points. The benefit of use of analytic strategies, such as responder analyses, is still uncertain.

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Since 1996, 38 placebo-controlled trials enrolling more than 100 participants have been conducted evaluating therapies in amyotrophic lateral sclerosis (ALS) (**Table 1**).[1-37] Of these, 6 studies[2,6,27,33,34,37] reported statistically significant evidence of efficacy. The first study to demonstrate efficacy was that of riluzule,[2] for which a survival association was noted in a large study of more than 900 participants observed for up to 18 months. This study led to the approval of riluzole by regulatory agencies in North America and Europe. One study[6] noted an association with 1 of 2 primary outcome measures, without discussion of how the α level was divided between the 2 primary measures. A third companion study in which riluzole was included as background therapy showed no significant effect on any measure. A second study reported statistically significant efficacy in a subgroup of participants, with that subgroup defined while the study was ongoing.[33] The other 3 studies have been published since 2017[27,34,37]; these studies are characterized by a duration of active treatment of 6 months or less, markedly smaller sample sizes than previous studies, and the use of a functional end point as the primary outcome. Other recent studies have also used similar designs, without showing efficacy.[33,35,36,38] The most parsimonious explanation for these and other clinical trial failures in ALS is that the agents tested, in fact, were ineffective; in each of these instances, further development is being contemplated based on signals in biomarkers or post hoc analyses of subgroups. A discussion of the merits of potential therapeutic targets is beyond the scope of this article. Rather, here we discuss aspects of trial design that may be important in discerning an efficacy signal if in fact there is one to be identified. To do so, we review the recent positive studies, as well as several recent studies where efficacy was not observed but for which there is continuing interest in further development. The goal is to discuss important aspects of trial design rather than to provide a systematic review of all recent ALS trials.

Observations/Discussion

Review of Selected Recent Studies

Edaravone was approved by the US Food and Drug Administration (FDA) in 2017 for use in all people with ALS. An initial study[23] used

Table 1. Amyotrophic Lateral Sclerosis (ALS) Trials Since 1996 With More Than 100 Participants

Agent tested	Source	Sample size, active No./placebo No.	Maximum disease duration	Primary outcome measured, mo	Primary outcome	Efficacy demonstrated
CNTF	ALS CNTF Treatment Study Group,[1] 1996	485/245	No criterion	9	Muscle strength	No
Riluzole	Lacomblez et al,[2] 1996	717/242	60 mo (Onset)	18	Survival	Yes
BDNF	BDNF Study Group,[3] 1999	748/347	No criterion	9	FVC, survival	No
Topiramate	Cudkowicz et al,[4] 2003	198/98	36 mo (Diagnosis)	12	Muscle strength	No
Creatine	Shefner et al,[5] 2004	50/54	60 mo (Onset)	6	Muscle strength	No
Xaliproden	Meininger et al,[6] 2004	581/286	60 mo (Diagnosis)	18	Survival, VC	Yes[a]
Xaliproden	Meininger et al,[6] 2004	804/406	60 mo (Diagnosis)	18	Survival, VC	No
Vitamin E	Graf et al,[7] 2005	83/77	60 mo (Diagnosis)	18	Survival	No
Celecoxib	Cudkowicz et al,[8] 2006	200/100	60 mo (Diagnosis)	1 y	Muscle strength	No
Pentoxifylline	Meininger et al,[9] 2006	199/201	48 mo (Diagnosis)	18	Survival	No
Minocycline	Gordon et al,[10] 2007	206/206	36 mo (Onset)	9	ALSFRS-R	No
TCH346	Miller et al,[11] 2007	442/111	36 mo (Onset)	6	ALSFRS-R	No
Creatine	Rosenfeld et al,[12] 2008	53/54	60 mo (Onset)	9	Muscle strength	No
IGF-1	Sorenson et al,[13] 2008	110/100	30 mo (Onset)	24	Muscle strength	No
Gabapentin	Miller et al,[14] 2001	82/81	36 mo (Onset)	16	Survival	No
Co-Q	Kaufmann et al,[15] 2009	110/75	60 mo (Diagnosis)	9	ALSFRS-R	No
Copaxone	Meininger et al,[16] 2009	184/182	36 mo (Diagnosis)	12	ALSFRS-R	No
Dexpramipexole	Cudkowicz et al,[17] 2011	75/27	No criterion	3	ALSFRS-R	No
Pioglitazone	Dupuis et al,[18] 2012	109/110	36 mo (Diagnosis)	18	Survival	No
Ceftriaxone	Cudkowicz et al,[19] 2014	340/173	36 mo (Onset)	1 y	ALSFRS-R, survival	No
Dexpramipexole	Cudkowicz et al,[20] 2013	474/468	24 mo (Onset)	18	ALSFRS-R, survival	No
Lithium	Morrison et al,[21] 2013	107/107	36 mo (Diagnosis)	18	ALSFRS-R	No
Olesoxime	Lenglet et al,[22] 2014	259/253	36 mo (Diagnosis)	18	Survival	No
Edaravone	Abe et al,[23] 2014	102/104	36 mo (Onset)	6	ALSFRS-R	No
NP001	Miller et al,[24] 2015	94/42	36 mo (Onset)	6	ALSFRS-R	No
Erythropoetin	Lauria et al,[25] 2015	104/104	18 mo (Onset)	12	Survival	No
Tirasemtiv	Shefner et al,[26] 2019	303/302	No criterion	3	ALSFRS-R	No
Edaravone	Edaravone (MCI-186) ALS 19 Study Group,[27] 2017	69/68	24 mo (Onset)	6	ALSFRS-R	Yes
Ozanezumab	Meininger et al,[28] 2017	152/151	30 mo (Onset)	12	ALSFRS-R, survival	No
Rasagiline	Ludolph et al,[29] 2018	127/125	36 mo (Onset)	18	Survival	No
Methylcobalamin	Kaji et al,[30] 2019	247/123	36 mo (Onset)	6	ALSFRS-R	No
Reldesemtiv	Shefner et al,[31] 2021	342/115	24 mo (Diagnosis)	3	SVC	No
Levosimendan	Cudkowicz et al,[32] 2021	329/167	48 mo (Onset)	3	Supine VC	No
Masitinib	Mora et al,[33] 2020	216/114	36 mo (Onset)	12	ALSFRS-R	Yes (in subset)
AMX0035	Paganoni et al,[34] 2020	89/48	18 mo (Onset)	6	ALSFRS-R	Yes
Mesenchymal stem cells	Cudkowicz et al,[35] 2022	95/94	24 mo (Onset)	7	ALSFRS	No
NP001	Miller et al,[36] 2022	70/68	36 mo (Onset)	6	ALSFRS-R	No
Methylcobalamin	Oki et al,[37] 2022	65/65	12 mo (Onset)	4	ALSFRS-R	Yes

Abbreviations: ALSFRS-R, ALS Functional Rating Scale–Revised; BDNF, brain-derived neurotrophic factor; Co-Q, coenzyme Q10; CTNF, ciliary neurotrophic factor; FVC, forced vital capacity; SVC, slow vital capacity; VC, vital capacity.

[a] In 1 of 2 VC analyses. No survival benefit.

fairly standard inclusion criteria (vital capacity [VC] >70%, time from first symptom onset <3 years; definite, probable, and laboratory-supported probable ALS by revised El Escorial Criteria[39]) and found a nonsignificant trend toward slower decline in ALS Functional Rating Scale–Revised (ALSFRS-R) score over 24 weeks. Post hoc analyses suggested greater differences between placebo and active treatment in those participants with more widespread disease and shorter time from first symptom at baseline. Based on these observations, a subsequent study was initiated enrolling only people with definite and probable ALS less than 2 years from first symptom to baseline.[27,40] This study showed a statistically significant reduction in disease progression in participants treated with edaravone, as well as a statistically significant effect on disease-related quality of life and a strong trend toward preservation of VC.

The inclusion criteria used in the second study resulted in both faster ALSFRS-R score progression and increased homogeneity; these 2 factors allowed for an effect similar to that noted in the subgroup analysis to meet statistical significance. The same effect was noted in VC, a secondary measure. The strategy of identifying a cohort of people with ALS that will progress rapidly and homogeneously with respect to ALSFRS-R score was also adopted in another recent positive study of AMX0035.[34] This study enrolled a

cohort of individuals with even faster-progressing ALS by further limiting participants to only El Escorial definite ALS,[39] the most diffuse phenotype, and disease duration of less than 18 months from symptom onset to baseline. As a result, rate of progression as measured by change in ALSFRS-R was 33% faster than what was seen in the placebo group of the second edaravone study.

Investigators studying the effect of methylcobalamin in ALS also followed a similar strategy. A large study[30] enrolled 373 participants with ALS within 3 years of onset and used a 12-week natural history phase before treatment to discern rates of progression. This study did not meet its efficacy goal overall; however, a post hoc analysis showed a nominally significant effect on people with ALS with onset within 1 year and with a demonstration of at least a 1-point decline in the ALSFRS-R in the natural history phase. Based on these observations, a much smaller study[37] of 130 participants with disease onset within 1 year and progression in the ALSFRS-R of at least 1 point in the pretreatment phase showed a highly significant 43% reduction in the decline of the ALSFRS-R over 16 weeks. As with the other programs just discussed, homogeneity in rate of progression was also improved in the most recent study.

The results of these studies demonstrate that both progression rate and homogeneity can be altered by use of specific inclusion criteria, and the identification of therapeutic efficacy can be facilitated as a result. Another ALS development program may have been influenced by these factors but in a negative way. Tofersen is an antisense oligonucleotide directed against superoxide dismutase gene 1 (*SOD1*), which contains gene variations in approximately 20% of cases of inherited ALS in the US. A phase 1/2 study suggested that, over the course of 3 months, treatment with tofersen at a dose of 100 mg slowed disease progression, and individuals with fast-progressing ALS showed the greatest benefit.[38] A subsequent phase 3 study estimated rate of progression before baseline and enrolled participants with broad criteria,[41] with the primary outcome analyzed specifically on those expected to have rapidly progressing disease. As this was a genetic cohort, duration of disease and El Escorial diagnostic category were not tightly controlled. Study results showed trends toward slower progression in treated participants in both groups, but neither met criteria for statistical significance. One reason for this may have been the inclusion criteria that was used; the use of prestudy disease-progression rates successfully identified participants with rapid vs slow disease, but the lack of stringent disease duration and diagnostic category criteria resulted in quite variable progression rates and slower progression than was expected in a well-defined cohort of *SOD1*-mediated ALS. Although it remains possible that the negative results of the phase 3 primary analysis represent simply a failure of efficacy, a recent report has suggested a profound effect of tofersen both when variability of progression is reduced by the use of demographic cofactors and when longer follow-up was assessed.[42] For all of the studies just discussed, the strategy of altering inclusion criteria to enroll a study population with very specific characteristics raises the question of generalizability of results. This is a concern to the extent that the study population reflects participants who are uniquely sensitive to a particular therapy. Although this is possible with any recruitment strategy, there seems to be no strong reason to think that individuals with faster-progressing ALS are pathophysiologically distinct from those with more slowly progressing disease. The goal here is to identify a cohort in whom an agent of potentially general import can produce a signal in a shorter time period with fewer participants than would otherwise be required.

In summary, the success or failure of a clinical trial to show an efficacy signal obviously depends on the characteristics of the therapeutic agent but can also be affected by trial design. In particular, choices in inclusion criteria that selectively enroll patients with faster- or slower-progressing disease, as well as those with greater or lesser homogeneity of disease-progression rates, directly influences the chances of an efficacy signal being discerned. All development programs discussed have demonstrated efficacy in small, single studies. The question of whether such a demonstration should warrant regulatory approval is one that we do not address here; rather, we discuss these results in the context of how trial design can influence study outcome.

Neurofilament and Its Use in ALS Trials

One reason for the slow development of new ALS therapies may be the lack of a fluid biomarker that could either identify disease earlier than currently possible, demonstrate target engagement, or be a sensitive and responsive indicator of disease progression. Biomarkers potentially could fulfil multiple roles in the context of trials. Biomarkers reflective of overall disease burden could potentially act as a surrogate for a clinically relevant outcome; however, this use requires extensive data showing that such a marker predicts relevant outcome, and failure of the marker to change predicts a lack of clinical response. Pharmacodynamic markers assess activity in disease pathways and are of particular use in early-phase trials intended to confirm specific target engagement. Such markers are in routine use but are outside the scope of this discussion. **Table 2**[34-36,38,41-43] summarizes the markers that have been used in recent ALS trials. Currently, the most promising marker is neurofilament. Neurofilament levels reflect ongoing neuronal or axonal injury and can be measured in either blood or cerebrospinal fluid (CSF). Both heavy-chain neurofilament (pNfH) and light-chain neurofilament (NfL) levels have been measured; neurofilament level is increased in patients with ALS compared with healthy participants or controls with neurologic disease,[44] and higher levels portend faster disease-progression rates.[45-48] Within patients, levels of neurofilament after symptom onset seem to be quite stable over time. Neurofilament levels are elevated in many other neurologic diseases, including multiple sclerosis (MS)[49,50] and spinal muscular atrophy (SMA).[51] As such, neurofilament level appears to be a general marker of neuronal injury without disease specificity. A recent clinical trial in SMA showed decline in neurofilament levels in association with efficacious treatment.[49]

These attributes suggest that neurofilament levels could be an important biomarker for ALS, and an agent that reduces levels could be assumed to be likely to show clinically important benefits. However, recent results in ALS trials suggest the need for caution. The phase 1/2 study of tofersen in ALS showed clear reduction in NfL level measured in the CSF of participants receiving active treatment as compared with placebo; clinical variables also suggested efficacy.[38] Reductions in NfL level were also noted in the phase 3 trial; in participants with both fast- and slow-progressing disease, NfL levels declined by 50% to 60% in those treated with tofersen, whereas levels in placebo-treated participants remained stable. Of special interest in this study, SOD1 protein levels in the CSF were also reduced by 60% to 70% as a function of tofersen treatment, suggesting the clear target engagement and biological impact of tofersen.

Table 2. Biomarkers Used as Efficacy Indications in Amyotrophic Lateral Sclerosis (ALS) Trials

Biomarker	Clinical trial	Treatment response
NfL + pNfH plasma levels[38]	Phase 1/2 tofersen in patients with *SOD1*	Reduction of neurofilament levels correlated with statistically significant clinical efficacy signals
NfL plasma levels[41]	Phase 3 tofersen in patients with *SOD1*	Reduction of neurofilament levels but changes in clinical efficacy signals not significant when compared with placebo at 6 mo
NfL plasma levels[42]	Phase 3 tofersen in patients with *SOD1*, 12 mo extension	Reduction of neurofilament levels and statistically significant clinical efficacy signals observed at 12 mo when compared with placebo group
NfL CSF levels[35]	Phase 3 mesenchymal stem cell treatment	Nonsignificant reduction of NfL in patients receiving stem cell treatment and nonsignificant clinical efficacy signals
MCP-1 and VEGF CSF levels[35]	Phase 3 mesenchymal stem cell treatment	Significant changes in CSF levels when compared with placebo group demonstrating impact of cell therapy. However, nonsignificant clinical efficacy signals
CRP plasma levels[36]	Phase 2B trial of NP001	High plasma CRP levels used for post hoc analysis, and this group exhibited significant slowing of clinical markers of disease progression when compared to placebo group
CRP and IL-6 levels in plasma and CSF[43]	Phase 2 trial of tocilizumab	Significant reduction of CRP and increase of IL-6 in both plasma and CSF in response to drug treatment when compared with control group. Trial not powered to study efficacy, but data indicate target engagement.
NfL and pNfH plasma levels[34]	Phase 2 trial of AMX0035 in ALS	Plasma pNFH not altered by AMX0035 treatment, but ALSFRS-R mean rate of change was reduced compared with placebo

Abbreviations: ALSFRS-R, ALS Functional Rating Scale–Revised; CRP, C-reactive protein; CSF, cerebrospinal fluid; IL-6, interleukin 6; NfL, light-chain neurofilament; pNfH, heavy-chain neurofilament; *SOD1*, superoxide dismutase gene 1; VEGF, vascular endothelial growth factor.

As noted previously, however, clinical efficacy signals were not statistically significant.

Finally, results in the opposite direction underly the need for caution in interpretation of neurofilament levels. AMX0035 showed a statistically significant efficacy signal with respect to change in ALSFRS-R score. However, measurements of NfL levels in the blood failed to show any impact of active treatment.[34] Given the inconsistency of the data just discussed, it is clear that neurofilament levels alone cannot be regarded as a surrogate for clinical efficacy.

Analysis Strategies for Established End Points

The ALSFRS-R score decreases steadily over time in most patients with ALS. Strategies discussed previously can affect the homogeneity of participant progression, as well as select for groups whose disease progresses more slowly or more rapidly. Although the scale comprises ordinal single items, the pattern of progression for most end points appears roughly linear, at least with respect to groups,[4,8,17] and it is most commonly analyzed as a continuous variable. The ALSFRS-R score is most commonly analyzed using group statistics, such as slope of the rate of decline or mean change from baseline to the end of a trial. Differences between slope and change from baseline are subtle. The FDA Guidance for Industry[52] recommends obtaining relevant outcome measures at baseline and at regular intervals throughout a trial rather than simply recording outcomes at study completion. Thus, as multiple longitudinal measurements are obtained, it is possible that a slope assessment could be more reliable than change from baseline, which is more anchored on 2 data points. However, either analysis is one of group means, therefore, that the entire study population is included in the analysis.

Other analyses can target specific groups of patients, ie, those who either reach a failure end point (time to event), or those who are designated as responders. The most obvious time-to-event end point is survival. Survival has been used as a primary end point in past trials and was the measure that led to approval of riluzole by the FDA. However, although ALS is a fatal disease, event rates during the course of most ALS trials are low, such that the statistical power survival is low, sample size is high, and study duration is longer than that required when ALSFRS-R score is the primary outcome. Interestingly, strategies to enroll patients with rapidly progressing disease as in the AMX0035 study resulted in a population with a significant death rate over the entire conduct of the trial, including both placebo-controlled and open-label phases. For this reason, a difference in survival was noted between participants originally randomly assigned to active treatment or placebo.

Other time-to-event end points can be established using the ALSFRS-R or other measures. In a trial of lithium carbonate in ALS, a time-to-event end point was used[53] using the ALSFRS-R. Patients participating in the placebo-controlled trial were switched to active treatment with lithium carbonate as soon as they experienced a decline in the ALSFRS-R of 6 points. The time of this event was recorded and served as the primary end point. At the first interim analysis after 84 participants had been enrolled, the time-to-event end point favored placebo over lithium, and the trial met predetermined cessation criteria. Similarly, the phase 3 trials of xaliproden conducted in participants concurrently taking or not taking riluzole used a decrease in VC of less than 50% as a primary outcome.[6,54] This event occurred with a frequency of 46.6% in placebo participants and 35.2% of those taking xaliproden alone, reaching statistical significance. Such a difference was not noted in the trial for which riluzole was background therapy, and regulatory approval was not achieved. The high event rates in both the lithium and xaliproden studies allowed either futility or efficacy to be established using these end points. An important point to be stressed is that converting continuous variables to events has the potential to lose information, as the rate of decline in those participants not reaching the end point is not evaluated. The only participants contributing to the end point are those in which the failure end point has been reached.

Responder analyses are, in some ways, the converse of time-to-event analyses, in that the subset of participants who are designated as responders are the only ones to contribute to the end point. To the extent that a therapy may affect a subgroup of participants only, this may be an advantage. Clearly, a therapy targeting a specific genetic subtype of ALS would most likely affect only those with that specific genetic variant. In this situation, a more efficient study design would be to only recruit those with the gene variant, rather than enrolling a wide population and using a responder end point to isolate those likely to benefit. However, if the group most likely to respond to a new therapy is not known, responder analyses can isolate a group of participants to the extent that they are equally represented in placebo and treatment groups. Both responder and time-to-failure end points are reductionist in their nature; if a therapy is effective, the effect could be quite general, but only those who either cross a failure threshold (time

to event) or who respond dramatically enough to meet the responder definition contribute to the end point.

Miller et al[24] performed a safety and preliminary efficacy study of 2 dose levels of NP001 vs placebo over 6 months of active treatment. Neither slope of decline of ALSFRS-R score or change from baseline to end of active treatment showed statistical significance or clear trends toward efficacy. In a post hoc analysis, responders were identified as those for whom there was no decline in ALSFRS-R score; the percentage of responders in the higher-dose group was more than twice that of placebo, although this comparison did not reach statistical significance. As a post hoc analysis, this finding served to generate a hypothesis, which was not confirmed in a subsequent study.[36] This finding may simply indicate lack of efficacy but may also reflect the sensitivity of a responder end point when relatively few participants meet the responder criterion.

The previous discussion illustrates the opportunities and challenges associated with time-to-event and responder analyses. In general, for agents expected to affect targets of general importance in most patients with ALS, analyses of group differences (slope or change from baseline) are likely to be both more meaningful and more powerful. However, if the population of patients likely to respond is a subset of the total enrolled, such analyses have the potential to identify such groups. To the extent that these subsets can be identified prebaseline, adjusting inclusion or exclusion criteria to select for them would be a preferable approach.

ALSFRS-R Assessment

The ALSFRS-R is a 12-item functional assessment that surveys capacity in fine motor activities, gross motor activities, and bulbar and respiratory function. Although the items are equally distributed among these domains, changes over time primarily occur in the gross and fine motor domains.[17,31] Quantitative respiratory assessment and dedicated bulbar function scales may be more sensitive to changes in these functional areas; however, many years of use have resulted in a clear understanding of its properties with respect to expected decline,[11,20] as well as its relationship to expected survival.[55-57] Concern has been expressed regarding whether the nature of the measure precluded the recognition of efficacy of new treatments.[58,59] However, in a fairly small study of 24 weeks' duration, a slowing in rate of progression of approximately 33% was statistically significant and associated with benefit in a quality-of-life scale and a trend toward benefit in pulmonary function. This effect was not large enough to be noticed by patients, and the point estimates of effect of the ALSFRS-R were similar to those observed for VC and quality-of-life scale (the 40-item Amyotrophic Lateral Sclerosis Assessment Questionnaire). The point estimate of effect on ALSFRS-R in the AMX0035 study was similar to that seen for edaravone.

Another concern recently raised has been whether the ALSFRS-R might be a poor scale in those situations where an experimental agent affected 1 aspect of patient function but not the items surveyed in the instrument overall. For example, a drug that selectively improved breathing but not fine or gross motor function might have a signal that was masked by lack of response in the subdomains that are unaffected by that drug. Van Eijk et al[59] proposed that this issue could be resolved by separate efficacy analyses performed on each subdomain, correcting for multiplicity. With multiple simulations, they provided data to suggest that when benefit of a drug is limited to 1 subdomain, separate analyses may be more powerful. However, differences in power were quite small, and such analyses allow for an interpretation of efficacy even if another subscore showed actual harmful changes of the drug. An additional filter accounted for this possibility but left open the question of how stringent to make this filter. Depending on where the cutoff for potential harm is set, the sensitivity of individual subdomain analyses can vary. Another factor not addressed by such a proposal is that individual subdomains of the ALSFRS-R vary greatly in the extent to which they participate in the decline of the total score over time. The fine motor function subdomain contributes to the decline in total score more than twice as much as the respiratory domain.[31,60] A drug affecting only respiratory function will be less likely to demonstrate efficacy whether the individual subdomain or the total score is analyzed. Although this represents a significant issue for the ALSFRS-R more generally, agents currently being evaluated in trials have no a priori reasons to affect 1 aspect of the ALSFRS-R more than another. Overall, it seems that, although the ALSFRS-R is an imperfect instrument, its use is not reducing our ability to observe substantial benefit in ALS trials.

Conclusions

In summary, this narrative review suggests that alterations of inclusion or exclusion criteria in clinical trials in ALS can meaningfully affect trial populations and enhance or hinder the observation of efficacy signals, should they be present. Neurofilament levels are modifiable by at least some experimental therapeutic agents, but the extent to which neurofilament changes should affect decisions in phase 3 ALS trials remains unclear. Innovative ways of using standard clinically relevant outcome measures to discern effects on trial subsets may improve trial sensitivity but in general are more likely to be useful in hypothesis generation. Advances in trial design and objective measurement, when combined with development of specifically targeted drugs linked to relevant biomarkers, can together lead to further improvements in ALS treatment.

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