

ALS Community Workshop: Therapy Development and Regulatory Pathways

A Summary Report to the Food and Drug Administration

Introduction

On July 12, 2018, The ALS Association gathered together more than 90 members of the ALS community, representatives from the Food and Drug Administration (FDA), representatives from the pharmaceutical industry, members of the clinical research communities, plus many more online, to discuss recommendations to the FDA on proposed revisions to the draft [Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry](#) (“draft Guidance”) (Appendix E). The workshop covered many issues relating to clinical trials and regulations that influence the structure of trials, the ease (or lack thereof) of participation for people with ALS and their caregivers, and, ultimately, the speed of drug development and the availability of new treatments for ALS.

Stephen Winthrop, MA, MBA, chair of The ALS Association’s Board of Trustees, is a person with ALS. He was diagnosed with the disease in 2013 and has, so far, participated in 23 clinical trials. When outlining the themes of the day, he noted that the changes suggested in the Workshop are both hopeful and grounded in solid scientific practice. He said: “We are really looking at a new landscape that has already been taking shape over the last three to five years in the ALS research world. We are talking about embracing best practices that are already in place. We are all for better science, stronger numbers and less statistical noise.”

The Workshop was organized around three topic panels, each featuring leaders from the clinical research community and people with ALS who worked on the [ALS community’s draft Guidance initiative](#) (Appendix D). Each panelist gave brief remarks and we heard many comments from people in the audience and people online.

The conversation was energized and constructive. The attendees spoke about the urgent need to find effective treatments. When patients are diagnosed with ALS, they are told they likely have two to five years to live. They will progressively lose all motor function and be completely dependent on caregivers for their survival. Clinical trial guidance, design, and execution must reflect this reality.

The conversation also revealed that burden-to-benefit ratio for many clinical studies seems unbalanced. Some trials ask for more time and inconvenience from participants and caregivers than they should. Other studies are valid, efficient, and respectful, and those best practices should be used more often across all trial sponsors.

The panelists and audience highlighted many straightforward improvements the FDA could make to its draft Guidance to ensure more effective trials, including the issue of

reconsidering the need for placebo arms in every ALS clinical trial. Below, we summarize the key points that emerged during each panel and provide specific recommendations to the FDA to clarify, expand upon, or emphasize in its Final FDA Guidance.

Panel 1: Addressing the Reality of ALS in Drug Development: Patient Experience and Benefit-Risk

This session included discussion on the following concepts: burden of disease and impact on daily living; benefit-risk calculations involving prognosis; disease heterogeneity; and risk tolerance and their implications upon patients' views on trial design and participation.

Key points:

- The scientific community may not be sufficiently sensitive to the concerns of the ALS community and the reality of the disease. When patients are diagnosed, they are told they likely have two to five years to live and will progressively lose all motor function and be completely dependent on caregivers for their survival. Enrolling in a trial means losing control over one's overall treatment, which is especially difficult with a fatal disease that may progress rapidly. Long trials and placebo arms are more burdensome in the ALS space than in some other diseases, given the progressive and ultimately fatal nature of ALS. In addition, multiple or lengthy clinic visits can create unusual caregiver and logistical challenges.
- People with ALS emphasized that their experiences, and the experiences of their caregivers, should be incorporated at the design stage to reduce the burden of trials (*e.g.*, cumulative length of assessments, telemedicine, less frequent and shorter clinic visits) and increase enrollment and retention. Every aspect of a trial (*e.g.*, medication administration, clinic visits, transportation, etc.) impacts caregivers and takes time away from their other responsibilities.
- The risk-benefit calculation should be influenced heavily by the progressive, often rapid, and invariably fatal course of the disease. More risk is generally accepted by people with ALS than industry trial designers and regulators may fully appreciate. Madeline Kennedy, RN, MSN, a panelist and person with ALS, said: "We deserve to have that opportunity to try new therapies. We are dying. We need to be more creative, more aggressive, and more flexible in the development of new treatment options."
- The scientific community should work to reduce the use of designs that prevent participants from taking FDA-approved medications that may reduce their symptoms or extend their life. Participants should not have to choose between a proven modest benefit and the chance of a large benefit, assuming the trial is designed to capture the incremental benefit of a new treatment addition.
- Panelists agreed that given the devastating nature of the disease, researchers should be encouraged to promote access, such as through open label extensions, expanded

access, companions studies, and other options discussed below in the study design and placebo section.

Recommendations:

- Final FDA Guidance should expand the description of the specific nature of ALS to include that ALS is uniformly fatal due to respiratory failure; most patients die within two to five years of symptom onset; and ALS is increasingly debilitating and shows heterogeneous progression. We recommend expanding Section II to address this issue.
- Final FDA Guidance should include a stronger statement regarding FDA's consideration of patient tolerance for risk (Section III.B.6).
- Final FDA Guidance should include a strong recommendation that people with ALS and their caregivers be consulted early in the trial design stage, especially concerning choice and range of outcome measures, access to approved medication, logistics, burdens of trial participation, and access to treatments after the trial. We recommend adding a new paragraph to Section III.B.1 to address this issue.
- Section III.B.3 should clarify that sponsors should consider the burden on patients when designing their study procedures and timing of assessments.

Panel 2: Outcomes - What We Measure and How

This session included discussion on the following core concepts: efficacy endpoints, patient-reported outcomes, and biomarkers and their implications on trial participation and design.

Key points:

- Our understanding of fluid biomarkers (any measurable substance in the body that can be tracked over time), such as those derived from blood, urine, or cerebral spinal fluid, is advancing, and their use in trials should be encouraged. Chairman Stephen Winthrop, MA, MBA, said: "We are hoping the final Guidance document will express how much the FDA encourages biomarker research as part of the trial development program." It was acknowledged there is a separate FDA guidance regarding validation of drug development tools, such as biomarkers; however, because biomarkers are central to ALS trials, this point should be re-emphasized in the final FDA Guidance.
- There are significant differences between the ALS community's Guidance and the FDA's draft Guidance. Specifically, the ALS community's Guidance discusses the respiratory measures that have already been validated, along with measures of muscle strength. In contrast, the FDA's draft only mentions survival and ALS Functional Rating Scale-Revised (ALSFRS-R) and states that there are no currently validated ALS surrogate endpoints that correlate or predict clinical benefit. This is a

crucial area where there needs to be clarification and some degree of coherence between the two documents.

- Surrogate markers are critical for shortening initial trials. Some markers are still in the development stage in ALS, and others are ready to be used more broadly.
- Outcome measures other than death and time to invasive ventilation should be part of the trial toolbox. As the standard of care improves, the length of trials that rely on survival as an endpoint and the number of required participants greatly increase beyond what is feasible or ethically justified.
- Target engagement markers in cerebral spinal fluid (CSF), blood, or measures in imaging scans can demonstrate changes or downstream impacts of a treatment in a much shorter timeframe and with a smaller cohort. This approach can be especially useful in early phase trials that are not powered to demonstrate statistically significant changes in function.
- It is possible to use different measures and markers to reduce participant burden. For example, wearable devices may offer people with ALS expanded opportunities to participate remotely in clinical trials, reducing the burden of participation.
- Patient-reported outcome measures have the potential to capture additional benefits not captured by ALSFRS-R.
- The predicted effect of a treatment should inform the choice of outcome measure, and the outcome measure should be paired with an appropriate trial design. Researchers should also understand likely progressions of their endpoints before constructing the trial to ensure trials are appropriately powered and balanced.

Recommendations:

- Final FDA Guidance should clarify its consideration of different efficacy endpoints, including encouragement of validating patient-reported outcome measures to capture benefits beyond the ALSFRS-R and survival. Section III.A.3 and Section III.B.2 appear to be contradictory regarding symptomatic endpoints.
- Section III.B.2 should discourage the use of survival as a primary endpoint, given the required number of participants, length of trials, and the number of patients who will have to die in the placebo arm before statistical power is achieved.
- Section III.B.5 should clarify the use of specific respiratory measures as surrogate endpoints. According to Section III.B.2, they do not seem to be considered valid to definitively demonstrate efficacy, but we know they are strongly correlated with survival and survival without invasive ventilation.
- Final FDA Guidance should more strongly recommend the use of biomarkers as exploratory or secondary endpoints.
- Final FDA Guidance should encourage shorter trials, when possible, which can be facilitated through a wider use of biomarkers and secondary endpoints.
- Final FDA Guidance should include encouragement for the use of remote monitoring, where applicable and validated, to reduce the burden of trial participation.

- Final FDA Guidance should emphasize the appropriate choice of endpoints and design, given the phase and purpose of the trial. A paragraph should be added to Section III.A.1 to clarify the types of endpoints and designs appropriate for early phase, non-definitive trials. Language from the last paragraph of the document in Section III.C.2 regarding the use of exposure response endpoints in early phase trials should be emphasized in Section III.A.1.

Panel 3: Study Design

This session included discussion on the following concepts: improved trial design, and how trials can better account for disease heterogeneity and the statistical complexities it can bring.

Key points:

- Chairman Stephen Winthrop, MA, MBA, stated: “There are often disconnects between the patient population and trial designers about barriers to entry, and how high they are. Conversation with patients can really break down those miscalculations, and trials would be faster and cheaper.”
- Trials must be designed to deliver a clear answer, whether positive or negative. A clear answer is more likely to emerge with a clear hypothesis of mechanism and the use of appropriate endpoints to determine whether the drug hit its target.
- Without encouragement from the FDA, companies may use traditional, less flexible designs and forego pre-competitive data sharing. Stephen Finger, Ph.D., a panelist and person with ALS, said: “While many companies are using innovative techniques, many more are not—they are using a cut-and-paste approach. The power of the Guidance is to encourage wider adoption of many of these more effective and patient-focused techniques.”
- Each aspect of study design should be based on sound design principles, not simply historical precedent. Sound design principles include the use and length of observation periods, exclusion criteria, and endpoints, and the rationale for these criteria should be communicated to patients.
 - Sponsors should be encouraged to broaden inclusion criteria and include patients later in their disease progression. In cases where that is not possible, they should use informed enrichment strategies that leverage existing data and are based on the specific nature of the disease and the goal of the trial.
 - When broad inclusion criteria are not feasible, companion studies may allow access to a wider population and patients later in their disease progression, while providing valuable information to sponsors.
 - Inclusion criteria are important characteristics of trials, both for patients and for sponsors, and should not simply be based on what has been the standard protocol in the past. One panelist gave an example that many trials exclude patients on noninvasive ventilation. However, research now shows that these

- patients can be included in trials without masking an underlying effect of a drug, given proper design considerations.
- Innovative trial designs, such as adaptive designs and platform and basket trials, offer benefits to speeding the testing of new treatments.
 - The ALS population is highly heterogeneous. Accounting for that heterogeneity in trial design may include prospectively identifying sample subgroups or stratifying participants based on predicted rates of progression or survival or selective biomarkers. These techniques can dramatically reduce the number of subjects, while maintaining power and reducing the length and cost of the study.
 - Large databases and predictive algorithms have advanced to the point that they are useful in predicting how people with ALS will progress. One panelist noted: “Given the impossibility of balancing treatment arms on all of the known prognostic factors, stratifying on predictions of survival or progression is highly beneficial. Along the same line, covariate adjustment can ensure unbalanced arms do not bias results.”
 - Algorithms using large databases to predict survival and progression have advanced to the point that they can support more efficient designs. For example, trials can stratify treatment arms based on predicted survival or progression. This approach requires fewer participants than trying to balance treatment arms with prognostic factors. See, for instance, Berry *et al.*, [“Improved stratification of ALS clinical trials using predicted survival.”](#)
 - Especially for small trials that are not necessarily powered to identify efficacy using traditional measures, techniques such as Bayesian dynamic updating, the inclusion of prespecified secondary endpoints based on matched controls, or predictive algorithms can help clarify signals of potential efficacy.
 - Another application for predictive algorithms and matched controls from currently available databases is to increase the robustness of trial data and to help sponsors examine the representativeness of their placebo controls.
 - To summarize, one panelist suggested that given the devastating reality of ALS, when industry sponsors are designing trials, based on guidance from regulators, they should not make them unnecessarily burdensome; should not exclude patients without scientifically valid rationale; should use the best techniques available to provide clear answers in an efficient and expedient manner; and should be encouraged to provide access through the use of open label extension, small placebo arms, companion studies, and expanded access programs, when scientifically and financially feasible.

Recommendations:

- Final FDA Guidance should stress that the FDA encourages the use of flexible, innovative, and novel trial designs to reduce trial length, cost, size, and burden, while maintaining statistical power. We recommend the addition of a new paragraph to Section III.B.1 to address this issue.
- Final FDA Guidance should explicitly endorse the use of adaptive design and platform trials.

- Final FDA Guidance should encourage the use of stratification based on predicted survival or progression to ensure trial arms are appropriately balanced.
- Section III.A.2 should recommend the use of broad, informed inclusion criteria that enhances recruitment. It should also recommend the use of techniques, such as informed stratification and the use of exposure response endpoints, which facilitate broader inclusion criteria without sacrificing the statistical power of the trials.
- Section III.B.1 or Section III.B.3 should identify acceptable methods, other than placebo arms and taking repeated measurements in the clinic, to address disease heterogeneity. Approaches include the use of exposure response endpoints and the leveraging of outside data that can lead to shorter and more efficient trials.
- Final FDA Guidance should encourage the expansion of entry criteria to include more patients who are later in their disease progression, where possible, and should require an explanation for any exclusion and observation criteria.

Placebo Groups in Clinical Trial Design

There were some topics that were repeatedly raised throughout the Workshop. This section includes discussion on the following core concepts: the use of placebo in trials and increased access of investigational products.

Key points:

- Given the negative impact of placebo on recruitment and retention, companies should work to reduce the use and percentage size of placebo groups in their clinical trials, such as using disproportionate placebos (*e.g.*, 2:1; 3:1 test-to-placebo), whenever feasible.
- While people with ALS and their caregivers understand that definitive efficacy studies may require testing against placebo, they expect sponsors to match their trial designs with the purpose of the trial.
- Especially for early phase trials focused on safety or dose-response, placebo arms may decrease the efficiency of trials. Stephen Finger, Ph.D., said: “In these early trials focused on safety, we should be looking for effects that are significant or common enough that they should be obvious without a placebo. For a dose-response trial, if you are trying to distinguish the effects of multiple doses, it is more efficient to exclude a placebo. In terms of learning about efficacy in these small trials, we are not looking for a definitive answer, just an informative signal, which is more likely to come by leveraging external data.”
- While it may not be possible to completely eliminate placebo arms and 1:1 randomization designs, the size of the placebo arm may be reduced by increasing the power of the whole trial or reducing the required size of both arms. Predictive algorithms and matched controls can also help reduce the size of the required placebo arm.
- Given the progressive nature and severity of ALS, along with the lack of current treatment options, enrollment in a clinical trial should include the opportunity to

receive the experimental treatment being tested, whenever possible. Crossover designs, open label extensions, and expanded access programs can promote access to the experimental therapy and help increase potential benefit to trial participants.

Recommendations:

- Final FDA Guidance should expand the discussion of placebo use in III.B.1 to include the consideration of novel designs that reduce the size of the placebo arm through crossover designs, data-driven stratification, and disproportionate randomization. While the latter point is discussed in III.B.4.a, it should be addressed more directly.
- Section III.A.1 should address the necessity of placebo arms in non-definitive, early phase trials, including a discussion of when placebo controls may not be necessary in such studies.
- Final FDA Guidance should encourage sponsors to provide participants with access to active products, whenever possible. Post-trial access should be encouraged through open label extensions or expanded access programs.

Appendices

A: [Workshop Agenda](#)

B: [Panelist bios](#)

C: [Comments sent to the FDA Workshop inbox from the ALS community](#)

D. [ALS Community Developed Draft Guidance](#)

E. [FDA's Draft ALS Drug Development Guidance](#)

The recording of the Workshop can be viewed [here](#).