Summary of the Recommendations to the FDA

The Workshop was organized around three topic panels, each featuring prominent members of the clinical research community and people with ALS who have taken on a leadership role in the ALS community-led draft Guidance initiative.

Below are the recommendations to the FDA on its draft Guidance that are included in the report to the FDA:

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.

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.

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.

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.

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.

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.