

# ALS drug development guidances and trial guidelines

## Consensus and opportunities for alignment

Jinsy A. Andrews, MD, Lucie I. Bruijn, PhD, MBA, and Jeremy M. Shefner, MD, PhD

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### Correspondence

Dr. Andrews

ja2289@cumc.columbia.edu

## Abstract

The US Food and Drug Administration (FDA) developed a draft guidance for drug development in amyotrophic lateral sclerosis (ALS) that was issued in February 2018. The FDA draft guidance considered the recommendations developed by the ALS community that incorporated the views of a large group of clinical investigators, industry representatives, advocacy groups, patients, and caregivers. This external input from the ALS community reviewed the current state of clinical research in ALS, made suggestions over a wide range of drug development topics, and served as an educational tool to provide the agency with additional inputs about ALS, the state of the science, and the community's views on key topics. In parallel to this effort, there was an independent effort to revise and update the ALS Clinical Trial Guidelines. We discuss the areas of agreement of these 3 documents and the areas that provide opportunities to improve the efficiency of drug development in ALS. It is likely that further research into biomarkers, efficacy endpoints, and predictive algorithms will provide greater alignment among community stakeholders and increase clarity on drug development efforts going forward. Continued patient engagement and inclusion of patient experience data in every aspect of the drug development process will further facilitate the approval of new treatments.

## Introduction

Over the past several years, the US Food and Drug Administration (FDA) has increased efforts to integrate the patient voice into the drug development process. As part of this commitment, Patient-Focused Drug Development is an FDA initiative intended to bring patient perspectives at all stages of investigational drug development and the regulatory review process.<sup>1</sup> This initiative also aims to develop new assessment tools and clinical trial endpoints and to provide a framework to incorporate patient and caregivers views regarding the unmet need, what is clinically meaningful, and risk. The FDA has accepted externally developed guidance documents to obtain input from the community regarding disease-specific drug development. Although these documents are ultimately generated by the FDA, community and professional input is sought by the agency. With respect to amyotrophic lateral sclerosis (ALS), a recently completed a draft guidance for industry (Community Guidance; data available from Dryad, doi.org/10.5061/dryad.43qc486) incorporated the views of a large group of clinical investigators, industry representatives, advocacy groups, patients, and caregivers. The Community Guidance reviews the current state of clinical research in ALS and makes suggestions over a wide range of drug development topics. The Community Guidance included content that goes far beyond what typically is found in an FDA draft drug development guidance document in order to serve as an educational tool and to provide the agency with additional inputs about ALS, the state of the science, and the community's views on key topics.

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From the Eleanor and Lou Gehrig ALS Center (J.A.A.), Columbia University, New York, NY; ALS Association (L.I.B.), Washington, DC; and Department of Neurology (J.M.S.), Barrow Neurological Institute, University of Arizona College of Medicine, Phoenix. Dr. Bruijn is currently at Bruijn-Yard Neuroscience R&D Consultant.

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## Glossary

**ALS** = amyotrophic lateral sclerosis; **FDA** = Food and Drug Administration; **PCAC** = Patient and Caregiver Advisory Committee.

This community guidance was submitted to the FDA, which in turn developed an FDA draft drug development guidance document for public comments that responded in part to the community guidance.<sup>2</sup> Although nonbinding, FDA guidance documents can be highly influential. Developed for industry, FDA staff, and other stakeholders, the document is intended to provide clarity in key areas: content and evaluation of applications for products, manufacturing standards, testing of regulated products, and inspection and enforcement.

Independent of but parallel to the guidance development process, ALS clinician investigators initiated the update and revision of the previously published ALS Clinical Trial Guidelines.<sup>3</sup> This revision, published in *Neurology*,<sup>4</sup> was created with a formal consensus process that is not described here. The guidelines were conceived to guide industry and academic investigators in best practices for clinical trials.

The purpose of this discussion is to highlight the points of agreement among the 3 documents—the community guidance, the draft FDA guidance, and the Clinical Trial Guidelines—and to show specific points of nonalignment.

## Guidance development/methods

### Community engagement and development process

At a public hearing in 2013, the FDA encouraged the ALS community to develop a draft guidance to inform the development of an FDA-issued guidance document for drug development in ALS. Starting in 2015, ALS clinicians and researchers, patients, caregivers, advocacy group representatives, pharma, and federal government representatives from the NIH and Centers for Disease Control and Prevention began the process of drafting the community guidance. The project was governed by a steering committee made up of subject matter experts and representatives of key constituencies within the ALS community.

Seven working groups (benefit-risk, public policy, diagnosis, natural history, clinical trial design and outcome measures, frontotemporal dementia and ALS, and biomarkers) were established to oversee and develop specific chapters of the guidance. Each working group had representation from a variety of perspectives and included at least 1 person with ALS. As content was developed, it was periodically reviewed by the steering committee. The preliminary guidance document, which was shared with the greater ALS community in May 2016 for input during a 30-day public comment period, was

revised and submitted to the FDA in September 2016 and docketed by the agency in November 2017.

Importantly, a Patient and Caregiver Advisory Committee (PCAC) was established to work closely with the steering committee and working groups to provide patient perspectives. The PCAC provided comments and suggestions on every aspect of the guidance development. Participants on the PCAC included nearly 40 people with ALS, caregivers, family members, and individuals from other ALS organizations. The final Community Guidance was posted on the Public Docket in November 2017.

### Community Guidance

The draft guidance developed by the ALS community is a detailed document that reviews the state of knowledge regarding pathophysiology, genetics, and disease course in ALS; however, specific recommendations are embedded within the document as Proposed Guidances, which were intended as specific suggestions to which an FDA response was requested. Briefly, the major topics included the following:

1. Patients with ALS in general are willing to accept more risks than other patient groups with regard to testing new therapies and would regard nontraditional endpoints as potentially compelling.
2. New endpoints, including respiratory measures, muscle strength, and disease progression markers yet to be validated, should be considered as phase 3 clinical trial endpoints. Specifically, survival was viewed not to be an ideal clinical trial endpoint because its use mandates large, long duration trials.
3. The development of surrogate endpoints or intermediate clinical endpoints is encouraged; to the extent that they reliably predict important clinical outcomes, these endpoints should be acceptable to support accelerated approval.
4. While the design of predictive algorithms remains an active area of research, late-phase trials should still involve the use of a concurrent randomized control group.
5. Inclusion criteria should be as broad as possible, both to increase access to trials and to maximize generalizability of results.
6. Expanded access programs should be considered, especially for patients not eligible for most clinical trials. These programs should be implemented earlier in the development process than has traditionally been the case.
7. Genetic stratification should occur in all trials because differential efficacy based on genetics may occur even with agents not specifically aimed to target a single gene. This should occur in the context of a robust genetic counseling program.

## FDA draft drug development guidance

The FDA draft guidance for drug development, issued in February 2018, considered the ALS community recommendations above. It is important to recognize that the FDA guidance is not a legally enforceable document. Instead, the draft drug development guidance is intended to describe the agency's current thinking on a topic and should be viewed as recommendations. This document highlighted the following considerations:

1. The FDA specifically recognized that the progressive and ultimately fatal nature of ALS may affect considerations of risk and tolerance of new medications, consistent with the Community Guidance.
2. There is heterogeneity among the ALS patient population. If an investigational drug is expected to be generally effective in ALS, then the study should include a broader ALS population. The FDA supported the use of targeted subgroups as long as there was a scientific justification such as a drug targeting a specific gene or disease mechanism not expected to be present in all patients.
3. Measures of efficacy should always include mortality for considerations of both safety and efficacy. A mortality endpoint should always include the need for permanent assisted ventilation. Mortality is a potentially approvable endpoint, as are functional scales such as the Amyotrophic Lateral Sclerosis Functional Rating Scale–revised or the Appel Rating Scale. No other existing measures are mentioned, although the guidance does not rule out measures to be developed in the future.
4. The FDA recognized the typically rapid progression of disease in patients with ALS and suggested that study duration should be “practicable,” even if this results in only a modest beneficial effect. With regard to surrogate endpoints, the lack of credibility of current potential surrogates is mentioned such that, while opportunities for the use of surrogate endpoints to support accelerated approval may exist in the future, this is not currently the case.
5. Although the use of predictive algorithms is not specifically mentioned, the FDA document encouraged the use of all methods that effectively ensure the equivalence of treatment and control groups. Any use of historical controls, whether in the context of a predictive algorithm, was strongly discouraged.

## Alignments and divergences of the community guidance, FDA draft drug development guidance, and the ALS Clinical Trial Guidelines

### Alignment

#### Risk-benefit considerations

The FDA draft drug development guidance acknowledges that when making regulatory decisions about drugs to treat

ALS, the FDA will consider patient tolerance for risk and the serious life-threatening nature of the condition. This aligns with the Community Guidance, which specifically discusses risk-benefit assessment and the need for appropriate balance between the increased tolerance of people with ALS for drug development risk, given the prognosis, and the continued protection of people with ALS from their potential exploitation.

#### Heterogeneity (clinical trial population)

All of the documents generally agree that the ALS population is heterogeneous. However, the Community Guidance details specific issues related to disease heterogeneity and specific subpopulations of patients with ALS.

The FDA draft drug development guidance also discusses trial eligibility criteria as they relate to subpopulations and affirms that drug development can be targeted to an identified ALS subgroup or to ALS variants when scientifically justified. However, if an investigational drug is expected to be generally effective, then a broader patient population needs to be studied. Of note, however, the approval of edaravone to treat patients with ALS applied to all patients with ALS despite the use of stringent eligibility criteria in the clinical trial.<sup>4</sup>

#### Efficacy endpoints

All of the documents agree that favorable effects on function and survival can establish efficacy in patients. Although the FDA draft drug development guidance generally states that efficacy should be established by demonstration of a clinically meaningful effect on symptom or function or a favorable effect on survival, there is emphasis on survival as an essential endpoint, differentiating it from the other documents. The FDA draft drug development guidance asserts that functional endpoints can be confounded by missing data and death. Given this vulnerability of functional endpoints, the FDA guidance recommends using an analysis method that combines survival and function into a single overall measure such as the joint rank test.<sup>5</sup> The ALS Clinical Trial Guidelines and the Community Guidance also view this combined endpoint for clinical trials as acceptable.

The FDA draft drug development guidance also favorably discusses time to event endpoints, for which the event represents clinically meaningful worsening of disease. This also allows the possibility of transitioning patients to open-label treatment once a predetermined event has occurred. In addition, the Community Guidance highlights time to event endpoints as a means to shorten trials if sufficient events occur.

Both the ALS Clinical Trial Guidelines and the Community Guidance suggest a spectrum of functional endpoints that might support approval, but the FDA draft drug development guidance does not mention specific functional endpoints. Instead, it states that new endpoints that demonstrate meaningful functional changes may be considered as potential phase 3 endpoints.

## Pharmacokinetics/pharmacodynamics

All 3 documents are similar in their discussions of nonclinical and clinical pharmacology studies. Both the FDA draft drug development guidance and the Community Guidance note that chronic toxicology studies can delay development timelines and prevent open-label extension protocols.

The FDA draft drug development guidance notes that it may be appropriate to initiate clinical trials on the basis of less-than-usual nonclinical testing if scientifically justified for serious and life-threatening diseases for which treatments are not available or are inadequate. It also discusses that the duration of dosing in humans may exceed that of the nonclinical studies if justified by the available nonclinical and clinical data.

In addition, the FDA draft development guidance suggests that carcinogenicity studies can generally be conducted after approval for drugs intended to treat ALS, given the unmet need for effective therapies. Other human clinical pharmacology studies such as renal or hepatic studies may be waived if the patient population and the metabolic pathways of the drug suggest a low likelihood of clinically meaningful pharmacokinetic and pharmacodynamic effects.

## Divergence

### Study design

The FDA draft drug development guidance strongly recommends that sponsors conduct randomized, placebo (or standard of care)-controlled double-blind studies because these studies are the most efficient way to demonstrate efficacy. The ALS Clinical Trial Guidelines and the Community Guidance also emphasize that randomized controlled trials remain the most robust way to demonstrate efficacy. However, these 2 documents emphasize the need for flexibility and innovation in clinical trial design, including unequal treatment groups and multiple drug comparisons. Overall, each of the documents highlights the potential utility of an adaptive clinical trial design.

The FDA draft drug development guidance strongly discourages the use of historical controls. Both the ALS Clinical Trial Guidelines and the Community Guidance are less prescriptive and suggest the possibility that well-matched historical controls may provide useful comparator information for middle-stage trials.

Predictive algorithms are not discussed in the FDA draft drug development guidance but are another avenue by which historical controls may be used. The ALS Clinical Trial Guidelines emphasize the potential utility of technology assisted measurements as exploratory endpoints. The Community Guidance notes that although the Center for Devices and Radiological Health has qualification requirements for technology-assisted measurements,<sup>6</sup> the Center for Drug Evaluation and Research has no such guideline. The Community Guidance also suggests that predictive algorithms

could be explored in the middle phase of trials and that similar algorithms could be used to efficiently stratify patients for clinical trials.

### Endpoints

The FDA draft drug development guidance is more stringent regarding efficacy endpoints than the other documents. As noted above, both functional and survival endpoints are endorsed with an emphasis on survival. A variety of secondary endpoints are proposed to support survival or functional endpoints.

The Community Guidance also endorses survival as sufficient to support approval of an investigational drug for ALS. However, other endpoints are felt to be more appropriate because a survival endpoint would require long-duration studies with large sample sizes. Trial duration and sample size are major drivers of cost and clinical trial efficiency. The ALS Clinical Trial Guidelines also suggest a variety of nonsurvival endpoints to support approval and note that neither survival nor the more commonly used rating scales are sensitive endpoints in phase 2 studies. For these reasons, the ALS Clinical Trial Guidelines and the Community Guidance support the continued study and potential use of a variety of measures assessing motor strength and functional capacity in future middle- and late-phase clinical trials.

The FDA draft drug development guidance discusses quantitative endpoints for strength and respiration but suggests that results can be affected by patient motivation, effort, and expectation bias. This is in direct conflict with the other documents, which express the strong view that quantitative measures of muscle strength and pulmonary function should be considered adequate to demonstrate efficacy in future clinical trials because they are well characterized and reproducible across many prior ALS studies.

Reassuringly, the FDA draft drug development guidance states that the FDA will consider proposals for the use of new outcomes measures that are capable of measuring clinically meaningful effects in patients.

### Accelerated approval

The FDA draft drug development guidance differs from the other documents in its view of the accelerated approval process and suggests that the rapid progression of disease in ALS renders accelerated approval unnecessary. The lack of credible surrogate endpoints is also cited as limiting accelerated approval. The Community Guidance and the ALS Clinical Trial Guidelines acknowledge the lack of clear surrogate markers but view such development as critical to more efficient trials. Thus, although the documents differ in tone, recommendations for the use of surrogate markers do not diverge.

## Omission

The FDA draft drug development guidance makes no mention of issues specific to ALS when conducting studies that involve cell therapy or gene therapy. Specifically, there is no discussion of study populations, use of control arms, or considerations regarding safety and efficacy despite several investigational stem cell- and gene-directed studies entering early-phase clinical development in patients with ALS. In addition, the FDA draft drug development guidance does not discuss considerations regarding studies targeting a specific gene mutation in familial ALS that would involve small numbers of patients and may preclude standard trial designs. The topic is discussed in detail in both the Community Guidance and the ALS Clinical Trial Guidelines. However, there is a general guidance for industry regarding cell and gene therapy provided by the FDA that discusses this topic more broadly.<sup>7</sup>

## Discussion

Overall, there are key points to which all of the documents align. One major area addressed in the FDA draft drug development guidance is the flexibility in nonclinical and early clinical pharmacology studies. This flexibility in nonclinical studies such as clinical pharmacology, chronic toxicology, and carcinogenicity studies will provide more efficiency of moving investigational drugs forward to human clinical trials. However, once an investigational drug is ready for phase 3 testing, the FDA draft drug development guidance does not suggest outcome measures other than those used for the past several decades. Using these same endpoints will continue to make ALS therapeutic development slow and inefficient. However, it is encouraging that the FDA is willing to consider novel functional outcomes. The tasks of validating and demonstrating clinical meaningfulness of any new measure will be critical for the ALS community.

Although the waivers for some clinical pharmacology studies such as hepatic or renal studies may reduce a portion of clinical development time, the effect on overall efficiency will be small. The FDA draft drug development guidance acknowledges that long duration and large sample sizes in phase 3 studies impose burdens on the conduct of clinical trials and mentions that some existing outcome measures may be considered sufficient for approval.

Several major gaps need to be addressed to facilitate more efficient clinical trials in patients with ALS. Continued work is necessary to develop surrogate markers of clinical benefit that satisfies the requirement of the regulatory criteria. It will be a challenge to conduct a clinical trial of an investigational drug that can achieve accelerated approval without these credible surrogate markers. The Community Guidance and the ALS Clinical Trial Guidelines highlight various potential surrogate markers, but further work is needed to establish credibility of potential surrogate endpoints that is reasonably likely to predict clinical benefit to serve as a basis for accelerated approval.

All of the documents also agree that randomized, placebo-controlled, double-blind studies are the most robust to demonstrate efficacy of investigational drugs. However, predictive algorithms using historical data may be scientifically valid both for improved stratification and to generate comparators in earlier-phase trials. Further work is needed to identify the ideal role of historical controls and predictive algorithms in the course of clinical drug development.

Finally, several outcome measures highlighted in the Community Guidance and the ALS Clinical Trial Guidelines assess quantitative muscle strength or pulmonary function. The FDA draft drug development guidance does not address these endpoints and suggests that these measures are not sufficient to support approval of an agent. It is therefore left to investigators to perform studies to demonstrate the relationship of these endpoints to outcomes that are considered to be clinically relevant by regulators, investigators, and the patient community.

## Conclusion

The development of a Community Guidance in parallel with the updated ALS Clinical Trial Guidelines brought together a diverse set of stakeholders in the ALS community and enabled the sharing of the most recent science and open dialog and debate in many of the challenging areas. While there were many areas of agreement, there is lack of consensus on a variety of issues that could improve the efficiency of clinical trials. It is likely that further research into biomarkers, endpoints, and predictive algorithms will provide greater alignment among community stakeholders and increase clarity in drug development efforts going forward. Continued patient engagement and inclusion of patient experience data in every aspect of the drug development process will further facilitate the approval of new treatments.

## Author contributions

J.A. Andrews: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval. L.I. Bruijn: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and will give final approval, study supervision. J.M. Shefner: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and will give final approval.

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## References

1. Food and Drug Administration. CDER patient-focused drug development. Available at: [fda.gov/Drugs/DevelopmentApprovalProcess/ucm579400.htm](http://fda.gov/Drugs/DevelopmentApprovalProcess/ucm579400.htm). Accessed June 6, 2018.
2. Food and Drug Administration. Amyotrophic lateral sclerosis: developing drugs for treatment, draft guidance for industry. Available at: [fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596718.pdf](http://fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM596718.pdf). Accessed June 6, 2018.
3. Miller RG, Munsat TL, Swash M, Brooks BR. Consensus guidelines for the design and implementation of clinical trials in ALS: World Federation of Neurology Committee on Research. *J Neurol Sci* 1999;169:2–12.
4. van den Berg LH, Sorensen E, Gronseth G, et al. Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials. *Neurology* 2019;92:e1610–e1623.
5. Writing Group; Edaravone (MCI-) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16:505–512.
6. Berry JD, Miller R, Moore DH, et al. The combined assessment of function and survival (CAFS): a new endpoint for ALS clinical trials. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14:162–168.
7. Food and Drug Administration. Medical device development tools: draft guidance for industry, tool developers, and Food and Drug Administration staff. 2015. Available at: <https://www.fda.gov/media/87134/download>. Accessed June 6, 2018.
8. Food and Drug Administration. Considerations for the design of early-phase clinical trials of cellular and gene therapy products, guidance for industry. Available at: [fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf](http://fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf). Accessed June 6, 2018.

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