Day 1 | Introduction and State of Research and Drug Development

Introduction
Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disease; most cases of ALS are sporadic with no known cause or cure. Approximately 5,000 people each year are diagnosed with ALS and, while disease natural history and pathogenesis are incompletely defined, disease progression is often characterized by progressive muscle weakness with death occurring, on average, three to five years after disease onset due to ventilatory failure. With only two FDA-approved therapeutics with limited benefits, there is a large unmet medical need in therapeutic development for ALS. Standard of care for most patients is comprised of symptom management and respiratory support via a multidisciplinary care team.

Although there has been progress in basic and preclinical research for ALS over the last two decades, there are numerous challenges impeding drug development in ALS, including gaps in disease characterization, due in part to disease heterogeneity and complexity, the lack of diagnostic biomarkers for the disease, and difficulties with patient enrollment in clinical trials. Researchers are continuing their work to develop and validate more sensitive diagnostic and prognostic biomarkers in an attempt to support therapeutic development through better characterization of disease pathogenesis and natural history. Further, clinical trialists are exploring and implementing innovative approaches to clinical trial design, including platform and adaptive designs to maximize the statistical power of trials and to minimize study duration, risk to patients, and the overall number of patients required for trial conduct.

Researchers and trialists also continue to seek out more innovative approaches to capturing and incorporating patient-reported outcomes in trials and to maintaining and leveraging shared data through biomarker repositories, consortiums, and shared analytics platforms.

To support advancements in the design and conduct of clinical trials and to facilitate improved access to therapeutics for patients with ALS, the Robert J. Margolis, MD, Center for Health Policy at Duke University, under a cooperative agreement with the US Food & Drug Administration, is convening a workshop to discuss challenges to drug development in ALS and strategize about ways in which these barriers may be overcome. This workshop will explore topics and considerations related to:

- Priorities for basic, preclinical, and clinical research
- Challenges and scientific considerations associated with clinical trial design for ALS therapeutics
- Elicitation and integration of patient experience data in clinical development programs for ALS
- Applicability and feasibility of innovative trial designs for ALS trials
Session 1: Importance and Limitations of Basic and Preclinical Research

Although progress has been made, studies indicate that the drug development enterprise is underperforming with respect to the generation of effective ALS therapeutics, due in large part to inadequate disease characterization.\(^1\,^4\) Disease heterogeneity and gaps in knowledge about the genetic mutations associated with different ALS phenotypes impact the predictive validity of disease models, impeding overall ability to test investigational therapeutics. Impediments to the development of diagnostic, predictive, prognostic, and pharmacodynamic biomarkers to support therapeutic development include the impact of disease heterogeneity and confounding variables (e.g., gender, age, and ethnicity) on the ability to link markers to clinically relevant measures of disease presence or severity. Biological fluid-based markers and electrophysiological markers, such as motor unit number estimation (MUNE), motor unit number index (MUNIX), and compound muscle action potential (CMAP) show the most promise in supporting disease diagnosis, the monitoring of disease progression and the measurement of treatment effects, but much work on biomarker identification and validation remains.\(^4\,^5\,^6\)

Researchers, clinical trialists, and federal stakeholders each have a role in supporting the translation of findings from basic and preclinical research into advances in therapeutic development. The National Institutes of Health is focusing on adapting emerging tools and technologies to identify the causes of ALS on a molecular level and identifying biological similarities between ALS and other neurological diseases.\(^7\) Several public and private organizations have also collaborated to create biomarker consortiums, including biorepositories, to support biomarker validation and ALS therapeutic development.

In this session, participants will discuss the value of these efforts as well as gaps and challenges in basic and preclinical research, and the importance of collaborative approaches to addressing these issues to support drug development for ALS.

Discussion Questions:

1. What innovative approaches are being taken to accelerate drug discovery in ALS (e.g., novel ways to identify potential druggable targets) and how can the research community benefit from continued investment in this work?
2. How can the predictive validity of disease models be improved to better support the conduct of clinical trials?
3. What are the challenges associated with validating biomarkers, and what approaches may support efficient biomarker validation?
4. What is the role of pre-competitive collaboration in helping to streamline and accelerate basic and preclinical ALS research?

Session 2: Considerations for Innovative Trial Designs

Innovative trial designs may be helpful in accelerating therapeutic development for ALS. Platform trials with adaptive features show promise in supporting efficient evidence generation on the safety and efficacy of ALS therapeutics, key to addressing acute unmet medical need. Platform trials allow for the testing of multiple drugs and delivery routes simultaneously, decreasing the overall cost and burden of research and expediting definitive answers on therapeutic safety and effectiveness.\(^8\)

Trialists are also undertaking approaches to facilitate improved access to clinical trials across the ALS patient community, whose ability to participate in clinical research varies and is contingent on a number of factors. These approaches include decentralized trials to increase access and enrollment for patients who are not located near a research center, remote monitoring used alongside digital tools to reduce...
the need for travel for those with limited mobility, the design of trial randomization schemes to increase the number of participants able to access an investigational treatment during the trial, and open-label extension studies to provide expedited access to the trial drug for those randomized to a placebo comparator in placebo-controlled trials.

In this session, participants will discuss scientific and practical considerations for innovative trial designs in ALS drug development (e.g., approaches to increasing patient recruitment and enrollment, parameters associated with patient eligibility criteria, the use of digital tools to support data collection, the utility of remote monitoring, and the feasibility of decentralized trials).

Discussion Questions:
1. What steps can be taken to make therapeutic development for ALS more efficient while ensuring the collection of robust clinical data to support regulatory and clinical decision making?
2. What benefits can remote monitoring and decentralized trials bring to researchers and patients? What are the barriers to increasing the use of remote monitoring and decentralized trials?
3. What steps can be taken to increase patient enrollment in innovative clinical trials? What are successful examples of this? What are the barriers?
4. How can trials be designed to best support patient access and subgroup analysis?

Day 2 | Looking to the Future

Session 3: Research Infrastructure and Data Sharing for ALS
Enhancements to existing shared data infrastructure can support both preclinical and clinical research for ALS. For example, expanded contribution to centralized shared data resources (e.g., patient registries, biospecimen repositories) can facilitate better understanding and documentation of disease progression and response to treatment with a reduced total investment of resources. This information can be used to support innovation and efficiency in trial design and to inform targeted patient recruitment. Furthermore, enhancement of a shared data infrastructure can encourage collaborative research, support the ability of researchers to compare results across clinical trials, and can mitigate research risk and burden on individuals impacted by ALS.

Session participants will discuss the specific benefits of enhancing a shared data infrastructure to support disease characterization, biomarker development, and the capture, efficient use, and reuse of clinical data. Speakers will highlight approaches to improving the utility of shared data resources, including the prioritization of patient privacy and the implementation of common data elements, data collection standards, and methods for assuring data interoperability.

Discussion Questions:
1. What are the barriers to data sharing in clinical research for ALS and how can research consortiums and funders facilitate open data exchange?
2. How can researchers and trialists maximize the interoperability of data collected as part of preclinical studies and clinical trials for ALS?
3. How can data sharing policies for federally funded research maximize the scientific value of clinical data collected as part of ALS trials?
4. What other mechanisms are needed to increase effective collaboration and minimize competition in ALS research?
Session 4: Understanding What is Meaningful for Patients - Recruitment, Patient Experience Data, and Expanded Access

The incorporation of patients’ experiences, perspectives, and priorities in drug development and evaluation supports the development of therapeutics with a meaningful impact on the quality and length of life for those impacted by ALS. Patient input should be considered throughout the product development lifecycle, particularly early on in the research and development process, including in trial design. To support the integration of patient input in trial design, trialists can elicit and incorporate patient and caregiver perspectives on several design parameters including the type, frequency, duration and overall burden of data collection required by the trial protocol, as well as trial enrollment criteria, and approaches to sharing trial data with patients, caregivers, and the broader clinical research community.

The patient voice should also be accounted for in the development of endpoints that are representative of clinically meaningful improvements for ALS patients, who have identified a need for therapeutics that slow disease progression, improve muscle weakness, and assist with breathing or respiratory function.11 There has been an increased focus on the need for measures of therapeutic benefit beyond mortality endpoints in clinical trials for ALS—for instance, measuring improvements in the functional status of patients as characterized by patient-reported outcomes. Finally, trials can be designed to minimize the number of patients randomized to the control arm, therefore maximizing the number of patients randomized to treatment arms. Additionally, open-label extension studies can be offered following the completion of randomized trials to allow access to investigational treatments to all trial participants. Industry, regulatory, and other stakeholders may also consider pathways outside of clinical trials for increasing patient access to investigational products, including through existing regulatory pathways such as FDA’s expanded access pathway (also known as compassionate use).

Participants will discuss approaches to the meaningful incorporation of patient input into clinical trial design and conduct, including approaches for eliciting patient input to inform endpoint development. Participants will also discuss effective approaches and challenges to increasing trial access and decreasing participant attrition.

Discussion Questions:

1. How can researchers better engage patients in the design of clinical trials?
2. How do researchers balance the needs of a trial while minimizing the burden on patients?
3. What are the barriers to the development and validation of novel endpoints that correlate to clinically meaningful benefits for ALS patients?
4. How can qualitative research contribute to improved patient-informed endpoint development?
5. What role can digital tools play in complimenting data collected through traditional clinical outcome assessments, including patient-reported outcomes (PROs)? How can patients and their caregivers play a role in collecting patient experience data that can inform ALS drug development?
6. What are the key considerations for the development and implementation of expanded access programs that allow access to therapeutics outside of traditional clinical trials?
Session 5: Coordination, Collaboration, and Shared Strategy
Discussion in this session will address next steps and stakeholder roles to support ALS research and therapeutic development. Participants will discuss feasible approaches to improving the quality and availability of shared data resources, models, and other tools to support disease characterization. Participants will also discuss priorities, roles, and responsibilities for advancing biomarker development and validation. Finally, participants will discuss next steps for maximizing the utility of innovative approaches to trial design to reduce research burden and increase access to therapeutics for individuals impacted by ALS.

Discussion Questions:
1. What are the next steps to accelerate ALS drug development? How do you envision the role of patient, industry, research, and regulatory stakeholder groups in advancing drug development?
2. To what extent is ALS research siloed and/or unnecessarily duplicative? If this is a problem, how can it be addressed?
References


