Worldwide Clinical Trials

Evaluation of the ALS Clinical Trial Landscape — Discoverability & Navigation

Lucie Undus, M.D
Executive Director, Therapeutic Area Medical Lead, Medical Affairs

Jeanine Ronniger
Senior Director, Project Management, Neuroscience

Debby Martin
Senior Director, Project Management, Neuroscience

Jeff Almrud, Ph.D
Senior Director, Project Management

Roberta OKelly
Executive Director, Project Leadership

Rich Bennett, BSc
Executive Director, Therapeutic Strategy Lead, Neuroscience

Amyotrophic Lateral Sclerosis (ALS), also known as motor neuron disease (MND) in some regions, is a rapidly progressing and invariably fatal neurodegenerative disorder that has risen in prominence within societal conscience because of hugely impactful awareness and funding campaigns such as the global reach of the ice bucket challenge, initiated by Pete and Nancy Frates with ALSA, or at the international level with iconic stories of ALS or MND impacting celebrities or sports stars.

Today, there is no cure for ALS/MND, with only modestly efficacious approved therapies available for most people living with ALS (plwALS). For example, tofersen, an ASO for SOD1-ALS, infers a greater treatment effect but is only relevant to people with this specific genetic form of ALS/MND (~1%). Due to clinical trial interpretation and the divergent regulatory sentiments, there is an inequity in access to approved ALS treatments across the globe.

There is an ongoing and desperate need for research and development of disease modifying therapies, making clinical trials an essential part of pharmacotherapy for ALS/MND, which forms part of the overall multidisciplinary care of plwALS alongside support such as physical therapy, speech therapy, nutritional and respiratory medicine.

Despite research advancements, access to clinical trials is limited, with a reported 5-10% of plwALS participating in clinical trials. Below, we explore factors that impact trial participation and considerations when seeking to reach and enroll qualified participants.

Factors Limiting Participant Access

The components of trial awareness and access are multifaceted and broadly span entry criteria, value proposition compared with current treatment, and geographical barriers. Understanding the influences can help ensure that these challenges do not interfere with participant access.

Entry Criteria

Because ALS is notoriously heterogeneous, trials can often attempt to minimize the impact on signal detection through defining entry criteria. These criteria are frequently very similar across all trials through entry criteria intended to behave as an enrichment strategy and thus contribute to the scientific validity of the study. With early phase clinical trials often conceited in signal detection despite being underpowered for clinical effect, the rise of neurofilament light chain (NfL) as a validated biomarker may both replace subjective measures and reduce the need for restrictive entry criteria in the future. Later phase clinical trials appropriately powered for clinical effect may be encouraged to represent the general population for intended use (generalizability) but early signals in specific sub-populations may translate to the incorporation of additional selection criteria.

Is the Participant Clinical Trial Ready?

- Fully aware of the trial protocol and what is required or expected
- Understands the terminology used
- Ready for the commitment
- Comprehends the benefit-to-risk profile
- Informed on data, health information, and biological sample use

My ALS Decision Tool™ — resource for learning about ALS clinical trial participation

The Balance Between Treatment, Motivation, & Burden

ALS patients and caregivers are subjected to significant daily burden while living with and caring for the progressive condition. This burden amalgamates with the fear of the unknown in symptom progression, overall prognosis, financial strain, and challenges in performing routine daily tasks. Thus, when considering trial feasibility, the proposed visit and assessments or procedure schedules in a clinical trial define a substantial degree of burden or strain associated with participation. While many actions can be taken to minimize these burdens, the nature of the tested drug or the assessments selected may limit the ability to use hybrid-decentralized trial techniques whereby the study can come to the participants' homes rather than requiring the participant to attend the clinic location on multiple occasions, in the face of progressive and significant disabilities (e.g., changes to ambulatory and ventilation status).

The level of invasiveness of assessments is a key factor. With the evolution of basic science and method/assay techniques, opportunities are coming for less invasive measurements with greater accuracy in ALS/MND clinical trials, such as a switch from cerebrospinal fluid to plasma sampling for the measurement of neurofilament light chain, a biomarker of neuroinflammation and neuronal loss, and hence a pharmacodynamic measure of disease progression which has risen in prominence in the field of ALS/MND. This surrogate marker of clinical efficacy is emerging as the key marker in Phase II proof of concept studies, allowing the trials to be more appropriately proportioned to avoid otherwise underpowered clinical measures such as ALSFRS-R or SVC in Phase II.

Geographic Barriers to Access

ALS trials intrinsically anchor patients to clinical sites under the supervision and medical oversight of the principal investigator. Therefore, study sponsors together with their contract research organization (CRO) partners select countries and clinical trial sites based on various factors, including regulatory authorization, budget, country or site prior performance in different trials, and the inclusion of key opinion leaders (KOLs).

With the prominence of some ALS-specialist physicians as clinical trial KOLs, many sponsor companies form relationships that dictate where studies will be placed. Often, the same select group of leading candidate sites is chosen, which creates competition between trials at relatively few sites. As a result, large geographical regions and competent ALS specialist centers are not able to offer an appropriate or adequate variety and volume of clinical trials to their patients.

While concierge travel and automated reimbursement support plwALS and caregiver or family attendance at studies, the distances participants are allowed to travel to sites described within study protocols may be limited — typically as an assumption that participants living within a previously specified perimeter this will help with retention, but often becomes an artificial barrier.

Moreover, trials should not underestimate the rapport between a plwALS and their diagnosing physician and multidisciplinary care team. However, plwALS are in tune with the research landscape, state-of-the-art technology, and advanced technologies that can seemingly provide a value proposition that potential participants appreciate through biological plausibility and the hope for a "one-and-done" administration

Typically, trial enrolment is investigator-led, meaning that participants would consider trials offered at their ALS center over travelling further for a specific advertised trial.

potentially through cell and gene therapy. Therefore, emphasizing the novelty of the science and methods may be a pathway for increased awareness, interest, and improved enrollment.

Clinical Trial Navigation & Retention

Online scrolling and dry information leave many questions unanswered and lack the interactive and guided process that a potential study partner should be afforded. The role of the clinical trial participant is, therefore, to have a personal advocate in this trial shopping process, guiding through the study evaluation process, to help understand which trials are available, what they require or involve, and whether one might be a suitable candidate for the trial, subject to investigator judgment of medical eligibility. Fortunately, ALSA and MyTomorrows have teamed up to provide clinical trial navigator support for plwALS in the U.S.

Participation is a team decision where the family and caregivers play a significant role in the study search, suitability evaluation, and confirmation of committed support to join and comply with the trial requirements. Caregivers are drivers of neurodegeneration study success and should thus be heralded and celebrated. Unfortunately, online tools and information often fail to provide sufficient details that can be translated to the caregiver or family facilitator, making this a critical hurdle to consider when addressing enrollment. It is, therefore, essential to provide the caregivers and family members with the following information:

- Frequency of in person visits
- Any long days that require overnight stays
- Addressing any support with technology
- Expectations for drug administration or any diary requiring caregiver involvement
- Collecting caregiver reported outcomes as relevant
- Highlighting support packages available to caregivers for participation

With disease progression often cited as a reason for withdrawal, study requirements should be aligned to the entry criteria, particularly if a particular segment of ALS patient is studied.

Whether the original motivation for participation was for therapeutic benefit or altruism, the ability to conform to protocol requirements in the face of increasing disability may place limitations on the ability to access the investigational product and the relative contribution of the clinical data within the study analysis plans. Study sponsors may employ decentralized clinical trial solutions, prioritized clinical assessments (ordered administration) or long-term follow-up techniques to keep the participant on IP for as long as feasible, with meaningful data contribution.

The Patient Path to Trial Discovery

Ensuring trial visibility and discoverability for plwALS requires strategic efforts. Traditional clinical trial awareness tactics such as print or paid media or online advertising typically have low returns in the ALS community, partially because it is a rare disease with limited ability to reach patients directly from promotion. Alternatively, using online communities would be a suitable location for awareness campaigns, though study sponsors seldom adopt this strategy. Taking this route, therefore, sets the trial apart from the otherwise crowded space.

Other methods to reach plwALS and raise awareness often include in-person dialogue, word of mouth, and working with ALS specialists who can provide space for a clinical trial at their centers and work directly with the patients already on-site. In addition, ALS consortia are a sound resource for clinical trial promotion, details, and updates, with several currently active across the world (Appendix I).

Beyond consortia, expert community leader webinars often serve an important role in amplifying current and upcoming clinical trials, making it essential for sponsors to ensure these groups are aware. For example, the ALS Therapy Development Institute (ALS TDI) holds regular webinars updating the community about current and upcoming trials and the HEALEY Platform, run by HEALY and Massachusetts General Hospital in partnership with the Northeast ALS (NEALS) consortium.

Beyond this, several online sources aggregate information from Clinicaltrials.gov. The benefits include consistency of key, objective information. However, the data presented do not foster an ongoing conversation or discussion, as would be found with consortia and patient advocacy groups. Appendix I displays a complete list of online sources.

Ensuring Trial Visibility

Optimal trial visibility requires attention to the study design; it is essential to craft patient-centric clinical trials that minimize invasiveness and maximize flexibility in participation to the degree possible while continuing to collect the clinical data necessary to test the study hypotheses. Outlining the methodological adjustments and operational solutions used to enhance the participant experience will help the audience understand the measures taken by the sponsor to optimize the study.

Incorporating the lived experience into the protocols and study materials is critical to ensure that the participants and caregivers feel understood. This approach ensures equity in access to clinical trials by considering the distribution of study sites and center selection with limited competition to speed up enrollment and ensure study offerings at ALS-specialized sites. In addition, it is vital to actively engage the patient advocacy groups (PAGs) to provide shared information with community leaders. Taking these steps fosters trust within the ALS community.

In addition, PAGs use patient-centric trial rankings that can be leveraged to increase trial visibility further, such as the I AM ALS PaCTD. These rankings typically employ a scoring system out of five possible points that weigh important patient criteria, underscoring the need to engage in proactive dialogue with these organizations to ensure a meeting of mutual expectations.

Conclusion

While ALS research is moving in a positive direction, information for plwALS regarding clinical trial involvement is still largely dispersed, and trials tend to converge. The resources that share information about clinical trials are not always global, and information is often scattered across the Internet.

Equally as geographically restricted are the online resources and tools designed to make ALS clinical trials discoverable since PAGs and consortia provide them, which have a regional influence. A common theme amongst the available online information is the aggregation from the clinicaltrials.gov registry. This ensures accuracy and consistency but emphasizes the need for frequent updates on on-site locations and contact details for a discoverable trial to result in participation.

Community events such as conferences and webinars remain the mainstay of ALS community information exchange, with some coverage of the latest news in the ALS community, specifically online media/patient community groups. Transparency in plans, decisions, and frequent updates provided by sponsors or leading community representatives enhance the trust and optimism offered by potential participants towards specific studies that they can then discuss with their caring physician.

In the face of such a devastating disease course, one seeks reassurance that the strength of rapport and trust between plwALS and their care team means that it continues to be the main entry point to clinical trial participation. The human element prevails in ALS research, and through taking a more tactical approach to clinical trial design and awareness, trials can increase their reach and make strides to improve enrollment, retention, and results significantly.

Appendix I: Patient-facing online resources providing information relevant to ALS clinical trial discovery

Source	Tool
NEALS	Trial Finder
I AM ALS Signal Dashboard	Treatments & Clinical Trials
European Organisation for Professionals and People with ALS (EUpALS)	EUpALS Trials
ALS Canada (ALS CA)	ALS CA Clinical Trials
MND Australia	MND Clinical Trials
MND Association U.K.	MND Treatment Trials
PACTALS	Ongoing Clinical Trials
TRICALS/ENCALS	TRICALS Trial Overview

About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications – from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers.

For more information on Worldwide, visit www.worldwide.com or connect with us on LinkedIn.