

These principles are drawn from the ALS Community Workshop that occurred in the summer of 2018 and ongoing conversations with people with ALS and the scientific community about clinical trials. Our primary goal is to develop effective treatments and quickly distribute them to people with ALS. To do so, clinical trials must be efficient, impactful and respectful. Below are the ALS clinical trial design principles that we would like trial sponsors, regulators, and funders to use.

ALS CLINICAL TRIALS SHOULD BE EFFICIENT

Experimental treatments need testing to determine their effectiveness and safety using the fewest possible participants, shortest length of follow-up, and least burden on participants. Approaches include:

- Developing and using valid surrogate endpoints and biomarkers when possible to measure impacts quickly and precisely.
- Minimizing undue regulatory oversight and processes. Until there are effective treatments for everyone, ALS requires speedy clearance with the minimum acceptable standard of evidence and safety for approval.
- Minimizing trial length by reducing trial size to the minimum required to obtain a clear answer and accelerating participation through inclusive enrollment practices and feedback from potential participants to minimize burden. Lengthy lead times for screening or other pretreatment activities, or survival as a primary end point are discouraged.
- Sponsors should use accelerated approval and other expedited regulatory processes whenever possible.

ALS CLINICAL TRIALS SHOULD BE IMPACTFUL

ALS Clinical trials should be designed to provide as much information and certainty as possible, using approaches such as:

- Clinical trial design should be based on the best science and methods available and not limited by regulation or precedent.
 - Enrollment criteria should be based on a clear rationale and preclinical data to ensure the correct study population. Simply adopting criteria from previous trials is not acceptable.
 - Many people with ALS want to participate in trials. Every effort should be made to be inclusive while ensuring the trial provides clear answers about treatment efficacy. Adaptive designs and other innovative practices from other disease areas should be used to conduct fast, impactful trials.
 - Clinical trial design should evolve and improve with the science rather than constrained by ambiguous regulatory processes.
- Trials should share their data and report both positive and negative results through mandatory posting on clinicaltrials.gov. Additionally, efforts like [PRO-ACT](#), and patient Global Unique Identifiers should be used to allow sharing de-identified clinical trial data and facilitate integration with other scientific resources.

ALS CLINICAL TRIALS SHOULD BE RESPECTFUL

We ask that clinical trial sponsors and regulators honor the wishes and perspectives of people with ALS and their caregivers, recognizing perspectives such as:

- Risk management: Until there are effective treatments, people with ALS are willing to accept more risk
 - Participants may be willing to accept higher levels of risk and be more open to sharing their data. Given adequate and appropriate informed consent processes, they should be allowed to do so by Institutional Review Boards and other regulators.

- Since the disease is relentlessly progressive and fatal, the entire ALS community is willing to accept approved treatments with more uncertainty and risk than would be typical in other disease areas.
- Self-determination: People with ALS are the experts on their disease, and the masters of their treatment
 - Trial participation should not interfere with the regular care of trial participants.
 - People with ALS are the experts in living with the disease. Clinical trial design should incorporate measures clinically meaningful to them.
 - Sponsors and regulators should offer maximum transparency about the clinical trial and regulatory review status to prevent patient and caregiver confusion.
 - ALS Focus – an ALS Association patient preference survey program, will serve as a tool for the FDA, clinicians and sponsors to empirically explore ALS community and trial participant preferences and desired outcomes.
- Burden: ALS clinical trials should minimize burdens of trial participation
 - People with ALS and caregivers should be consulted on trial design to minimize the risks, discomfort, loss of control, hassles, financial barriers and logistical challenges of trial participation.
 - IRBs, the FDA, funders and other oversight groups should favorably consider trial features designed to reduce burden on people with ALS and their caregivers.
 - Reduce the size and ratio of placebo groups and consider eliminating them completely when efficacy is not a trial outcome, and/or when additional natural history progression models, crossover studies, or other approaches provide informative comparative data.
- Access: Trial sponsors need to increase access to experimental treatments
 - Trial participants originally on placebo or who believe the treatment impacted their disease should have access receive the experimental treatment, through open-label extensions or expanded access options, provided that the additional access does not slow or reduce the impact of the trial itself.
 - Trial sponsors should strongly consider companion studies where patients ineligible for clinical trials assessing efficacy can still participate to provide safety and tolerability information.
 - The entire ALS community should have access to experimental therapies under clinical supervision, provided that the additional access does not slow or reduce the impact of the trial itself.
 - We appreciate the ethical challenges of spending resources on access to experimental treatments, when many families with ALS are already overwhelmed with the financial burden of ALS (loss of income, home modifications, copays, etc.). Providing financial support for access to experimental treatments could draw resources away from the broader community to the handful of people willing and able to take experimental treatment outside of a clinical trial. Additionally, there is the potential that trial sponsors may profit from experimental treatments by exploiting people with ALS. The Association will continue to explore this issue, while honoring the rights and wishes of people with ALS.

For more details, see [recommendations](#) on the FDA guidance and in the revised Arlie House [guidelines](#).

We thank all the participants in the FDA workshop for their advice and feedback on these principles.