This is a final draft of the ALS Clinical Trials Guidelines for which we would like to solicit your comments. Although we tried to make the document uniform, at this point the reference style varies from section to section. After the public comments phase ends on August 31st, we will undergo a highly structured modified Delphi process to reach a full consensus on the Clinical Trial Guidelines. Eventually they will be published in a scientific medical journal.

If you wish to make any comments, please email them to, guidelines.public.comments@gmail.com. There are eight major sections containing multiple recommendations. Please specify to which section and which background, rationale, or recommendations you are referring by using appropriate number systems, so we can respond accordingly. We appreciate your patience, as all investigators must reach a consensus before addressing your comments.

Abbreviations: [Evid] = evidence; [Prin] = principle; and [Infer] = inference

SECTION 1. Preclinical Studies

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1-1. Do we need efficacy signals from preclinical models or can we identify drugs for human trials based solely on disease mechanisms and biological hypotheses?

Background:

Drug discovery traditionally requires a demonstration of efficacy in disease models (1). This prerequisite arises in part from regulatory requirements and also serves to prioritize one therapeutic candidate for clinical testing above others, an important consideration given the limited number of patients diagnosed with ALS available for clinical trial enrollment. Nevertheless, demonstrations of efficacy in animal models have not led to successful therapies in humans.

The development of drugs for ALS has been hampered by animal models that do not reflect the complete spectrum of phenotypes present in this polygenic disorder (2) and by inconsistency in the design and execution of preclinical studies (3). Recently, our ability to model human disease using cell-based models with induced pluripotent stem cell (iPSC) lines, three-dimensional tissue models, and other complex in vitro systems has improved dramatically (4-6).
Such cellular model systems permit confirmation of target engagement but may not effectively model the complex pathophysiology of ALS (2).

**Rationale 1-1-1:**

The prioritization of new therapeutic candidates for human trials relies on robust preclinical efficacy data and fulfillment of other regulatory requirements (e.g., 7, 8) (PRIN).

**Recommendation 1-1-1:**

Investigators must provide a firm biological rationale for moving a therapeutic candidate into human trials in ALS. This rationale may arise from animal models or cellular models of ALS and/or from clinical data.

**Rationale 1-1-2:**

Animal models express a range of ALS-associated gene mutations and exhibit some of the pathological changes observed in familial and sporadic ALS, but no animal model fully replicates human physiology (9,10) (EVID). No single measure of therapeutic effect in animal models can be expected to predict efficacy in humans (PRIN). Support for a therapeutic candidate is enhanced by demonstrating beneficial effects across a range of outcomes, including motor or cognitive function, neurophysiology, histopathology, and survival.

**Recommendation 1-1-2:**

Investigators may support advancement of a therapeutic candidate by demonstrating therapeutic effects on phenotypical outcomes (e.g., motor or cognitive function, neurophysiology, histopathology) as well as on survival when using *in vivo* models of ALS.

**References:**

5. de Boer and Eggan, A perspective on stem cell modeling of amyotrophic lateral sclerosis. Cell Cycle. 2015 Dec 2;14(23):3679-88. PMID: 26505672
1-2. How can we enhance the predictive value of preclinical *in vitro* and *in vivo* models of ALS?

**Background:**

A variety of cellular and animal models of ALS pathogenesis have been produced and characterized (e.g., 1, 2). At present, these models focus almost entirely on inherited forms of ALS, since the genetic elements responsible can be recapitulated in a cell or animal system in the form of a transgene, or as a gene knock-in or knock-out. *In vitro* models have been developed using cultured cells from other species (i.e., primary culture from rodents) or from humans (immortalized cell lines, induced pluripotent stem cell (iPSC) derivatives). *In vivo* models have been generated from a variety of species ranging from yeast, worms, flies, zebrafish, mice, rats, pigs, dogs to non-human primates. Historically, high level transgene overexpression has been used to drive neurodegeneration within the lifespan of model organisms. However, this approach can result in emergent or irrelevant toxicities that can mislead therapeutics development (3).

**Rationale 1-2-1:**

Preclinical research is an essential means to assess potential efficacy as well as safety of therapeutic candidates (PRIN). This includes proof-of-concept studies as well as a range of nonclinical studies to satisfy regulatory requirements for allowing a new agent to be administered to humans. Standard requirements are i) single and repeat-dose toxicity studies, ii) pharmacokinetic, toxicokinetic, adsorption, distribution metabolism and excretion studies, iii) genotoxicity studies, and iv) safety pharmacology studies (4) (EVID). Preclinical research is conducted in wild-type animals and cells, and in models of human disease (4) (EVID).

**Recommendation 1-2-1:**

Investigators should use preclinical model systems for two purposes:

a. Assessment of efficacy (cellular and animal models of ALS)

b. Assessment of safety, toxicity, bioavailability and biodistribution (which can be conducted in wild-type animals and cells or in models of ALS)

**Rationale 1-2-2:**

Each of the available ALS model systems has different strengths and weaknesses in regard to its ability to recapitulate abnormalities at the molecular, cellular, and organismal level seen in human ALS (PRIN). Thus, screening for genetic modifiers is most effectively accomplished in lower organisms, while comparative anatomy and pathology are improved in higher organisms with motor systems more similar to humans (e.g., 5,6,7) (EVID).

**Recommendation 1-2-2:**

Investigators should focus on using the strengths of each model system (e.g., genetic modifier screening in flies or yeast; target engagement in human cells; physiology in mammals).

**Rationale 1-2-3:**
Current animal models exclusively utilize genetic lesions from inherited forms of ALS, which may or may not recapitulate events in sporadic ALS or even other forms of inherited ALS (1,5-7) (EVID).

**Recommendation 1-2-3:**

Investigators should prioritize development of animal and cellular model systems that recapitulate key pathologies seen in sporadic ALS, particularly cytoplasmic TDP-43 mis-localization.

**Rationale 1-2-4:**

ALS patient-specific iPSC-derived models have been recognized as a powerful tool for human disease modeling and drug screening. However, these models have a number of drawbacks including (i) non-uniformity of differentiation protocols across laboratories leading to phenotype variability; (ii) the embryonic nature of the cell types generated (motor neurons, astrocytes, etc.) in vitro; (iii) high inter-individual variability (2,8) (EVID).

**Recommendation 1-2-4:**

In relation to ALS patient-specific iPSC-derived models, investigators should:

a. Incorporate uniform differentiation protocols to improve reproducibility
b. Use cell lines from a sufficient number of participants per group for studies comparing disease to control
c. Use genetically matched (isogenic) mutation-corrected lines when applicable (with rigorous quality control including karyotyping)

**Rationale 1-2-5:**

*In vitro* models typically only involve one or at most two cell types, limiting the ability to study more complex non-cell autonomous contributions to disease (2) (EVID). Further, human iPSC-derived central nervous system cell types have a relatively immature status, which is a challenge when studying a late-onset disease like ALS (8). The generation of human iPSC-derived three-dimensional cultures, also referred to as organoids, is a rapidly evolving technology and may overcome such limitations in the future (9) (EVID).

**Recommendation 1-2-5:**

To enhance existing *in vitro* models, investigators should develop model systems with multiple relevant cell types in organoid-like or similar three-dimensional structures to improve cellular maturity and to study non-cell autonomous disease processes.

**Rationale 1-2-6:**

The ideal disease model would recapitulate both the authentic genetic lesion (patient-specific iPSCs, knock-in transgenic animals) and also the full spectrum of disease-relevant phenotypes (e.g., 3) (PRIN). At present there are no models that completely fulfill these criteria (e.g., 6) (EVID).

**Recommendation 1-2-6:**
Investigators should focus on generating animal and cellular models of ALS which best reflect the human genetic lesion in order to minimize the chances of studying and targeting phenomena that emerge solely from high-level transgene expression.

**Rationale 1-2-7:**

Pharmacodynamic measures are needed to confirm that a therapeutic candidate affects the intended biology and reaches its cell/tissue target at the intended concentration (EVID) (10).

**Recommendation 1-2-7:**

Investigators should develop preclinical pharmacodynamic and target engagement biomarkers for therapeutic candidates to inform the design of human trials whenever possible.

**References:**

2. Lee and Huang, Modeling ALS and FTD with iPSC-derived neurons. Brain Res. 2015 Oct 14 pii: S0006-8993(15)00740-4. PMID: 26462653
7. Casci and Pandey, A fruitful endeavor: modeling ALS in the fruit fly. Brain Res. 2015 May 14;1607:47-74. PMID: 25289585
8. de Boer and Eggan, A perspective on stem cell modeling of amyotrophic lateral sclerosis. Cell Cycle. 2015 Dec 2;14(23):3679-88. PMID: 26505672

**1-3. Methodological Rigor of Preclinical Therapeutic Studies**

**Background:**

The low reproducibility of preclinical data has been recognized as a major challenge in biomedical research (1). Like in many other disease fields, ALS research has been plagued by a lack of successful translation of treatment efficacy from animal models to clinical care of patients (2). While the reasons for this deficiency may be multifold, the ALS research community has recognized that methodological rigor in animal model studies is imperative for the advancement of translational ALS research. Accordingly, the community has developed best practice guidelines for preclinical animal model research, starting with guidelines for the appropriate use of the transgenic SOD1G93A mouse model (2-5).
ALS animal models have been developed in a broad range of species (e.g., 6), and harbor many disease-causative mutations identified in genetic studies of human ALS. Patient-specific model systems are also emerging, including induced pluripotent stem cell (iPSC)-derived cell culture platforms. Methodological advances in reprogramming efficiency, cell culture maintenance and gene editing technologies are promoting the utility of these iPSC-derived model systems in basic and translational ALS research (7,8).

**Rationale 1-3-1:**

New animal and cell-based model systems for ALS require in-depth characterization of phenotypes and endpoints, in relation to the human disease, to ensure that a given measurement reflects the intended biology (9,10) (PRIN). The use of appropriate genetic controls enhances the informative value of phenotyping studies (PRIN). When characterizing the phenotype of human iPSC-derived cell lines, it is important to control for variability due to the intrinsic genetic background of subjects through use of isogenic, mutation-corrected lines (when possible) (7) (PRIN).

**Recommendation 1-3-1:**

Investigators and research funders should commit effort, time and funds to characterize and validate the molecular, cellular and, if applicable, behavioral phenotypes of new ALS model systems.

**Rationale 1-3-2:**

Adherence to best practice guidelines (e.g., 2-5 and new guidelines to be developed) for the use of animal models in preclinical research enhances data accuracy (i.e., lack of bias) and precision (i.e., minimal experimental noise) (10) (EVID).

**Recommendation 1-3-2:**

Investigators should develop, publish and adhere to best practice guidelines (e.g., 2-5 and new guidelines to be developed) for the use of fully characterized ALS animal models in preclinical research.

**Rationale 1-3-3:**

Resource sharing, via deposition of ALS animal models (e.g., 11) and ALS patient-specific cell lines into public repositories, supports community-driven efforts aimed at characterizing and validating the phenotypes of new model systems and developing best practice guidelines for their use in preclinical research (10) (PRIN).

**Recommendation 1-3-3:**

Investigators should deposit ALS animal models and ALS patient-specific cell lines developed in their laboratories into public repositories following initial characterization. For patient-specific cell lines, appropriate language should be included in informed consent forms to enable resource sharing.

**Rationale 1-3-4:**
Preclinical in vivo efficacy studies need to be supported by statistical modeling and rigorous study design (10) (PRIN).

Recommendation 1-3-4:

Investigators should apply appropriate experimental design (e.g., replicating full experimental groups) and statistical analysis (e.g., acknowledging covariance among observations within a block) in preclinical efficacy studies.

Rationale 1-3-5:

Preclinical dose-ranging studies inform dose selection for clinical testing (10) (EVID).

Recommendation 1-3-5:

Investigators should examine dose-response relationships with a minimum of three doses in preclinical in vivo and in vitro efficacy studies.

Rationale 1-3-6:

Independent validation of therapeutic candidates enhances confidence in their efficacy (1) (PRIN).

Recommendation 1-3-6:

Investigators and research funders should commit effort, time and funds to independent preclinical validation studies of therapeutic candidates, and publish positive and negative results, ideally in a peer-reviewed, open-access format.

Rationale 1-3-7:

Transparent reporting of key methodological and analytical information about efficacy studies in model systems is a prerequisite for evaluating the reliability of study findings and facilitating independent validation studies (12,13) (PRIN). Many scientific journals and funding agencies have developed a core set of generalized (i.e., not model system-specific) standards for the reporting of methods, and these can be easily adopted (14) (EVID). Model system-specific reporting standards are expected to further enhance the interpretability, and thereby the scientific value, of preclinical studies (INFER).

Recommendation 1-3-7:

Investigators should adhere to general (e.g., 14) and, if available, model system-specific reporting standards for key methodological and analytical information about preclinical studies in research publications.

References:

1. Prinz et al, Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov. 2011 Aug 31;10(9):712. PMID: 21892149
9. Hatzpetros et al, C57BL/6J congenic Prp-TDP43A315T mice develop progressive neurodegeneration in the myenteric plexus of the colon without exhibiting key features of ALS. Brain Res. 2014 Oct 10;1584:59-72. PMID: 24141148
SECTION 2. Study Design. Biological and Phenotypic Heterogeneity

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2-1. Should eligibility criteria be restricted (newly diagnosed patients, familial ALS, cognitive impairment, patients at late stages; etc.)?

Newly diagnosed patients

Background:
Incident (new cases) have a worse prognosis than prevalent cases (old + new). Prevalent cases are generally younger and more likely to have a spinal presentation and slower progression ¹ (EVID). Prevalent cases are more likely to be present in a multidisciplinary clinic than in a population based setting. The difference of setting is associated with a difference in survivorship of about one year between the two groups ²(EVID). The difference is critical considering the short median survival time of ALS. On the other hand, patients who are in different stages of their disease will ask to be included in RCTs (PRIN).

Rationale 2-1-1:
Inclusion of many prevalent cases could decrease power in RCT (INFER).

Recommendation 2-1-1:
In RCTs investigators should enroll patients with clinically definite ALS, clinically probable ALS, probable ALS - laboratory supported, and clinically possible ALS, pending adjustment of the WFN diagnostic criteria, who have a short interval from disease onset to trial entry.

Familial Cases

Background:
Familial cases of ALS vary ³ (EVID). The preferred definition of a familial case, according to a recent survey of one hundred ALS experts, is a patient who has a first or a second degree relative with ALS ⁴. Familial cases have the same clinical presentation as sporadic cases.
Specific gene abnormalities will influence the clinical phenotype of ALS and influence prognosis (PRIN). Several studies indicate a role of C9orf72 in ALS prognosis: resources may be a limitation for genotyping subjects at RCT entry (PRIN).

**Rationale 2-1-2:**

Subjects with positive family history may have a different prognosis because of the underlying genotype (INFER)

**Recommendation 2-1-2:**

Clinical trialists should examine the effects of specific genotypes and phenotypes, including cognitive/behavioral changes upon the primary outcome measure to determine whether stratification is warranted.

**Reference**

FDA Guidance for Industry: E9 Statistical Principles for Clinical Trials September 1998

**Cognitive impairment**

**Background:**

More than 50% of ALS patients present with cognitive impairment when formally examined. Executive impairment at the initial visit is associated with higher rates of attrition due to disability or death and faster rates of motor functional decline (EVID). Individuals without neuropsychological deficits at baseline are likely to remain free of such deficits throughout their disease course (PRIN). In C9orf72 expansion, neuropsychological deficits and neurobehavioral changes are associated with a family history of a neurodegenerative disease processes, and with shortened survival. This suggests that pathological hexanucleotide C9orf72 expansion should be considered as a basis for stratification in RCTs (EVID).

**Rationale 2-1-3:**

The inclusion of subjects with cognitive impairment at baseline with a worst prognosis may affect the balance and results of RCT (INFER)

**Recommendation 2-1-3:**

Neurocognitive (in particular executive dysfunction), and behavioral impairments are important prognostic factors that should be used to stratify ALS patients at entry in RCT.

**Restricted Syndromes**

**Background:**

ALS generally presents with a focal onset followed by a specific spread with progressive regional involvement. Further, the mix of clinical signs of first and second upper and lower motor neurons necessary for a diagnosis of ALS, may be not fully present at the time of first assessment, which gives rise to a diagnostic delay for many patients. The clinical involvement
may be limited to UMN or LMN in some subjects in all clinical courses of the disease. Subjects who can be classified as EEC clinically-definite have a faster course of disease and EEC is indeed a prognostic indicator in most of the studies \(^8\) \(^9\) \(^10\) \(^11\) \(^12\) but not in all \(^13\) \(^14\). Conversely, the presence of pure UMN or LMN signs is associated with longer survivorship \(^2\) \(^15\) \(^16\) \(^17\) (EVID).

**Rationale 2-1-4:**

Restricted syndromes may have a better prognosis (INFER) compared to typical ALS

**Recommendation 2-1-4:**

Specific clinical phenotypes (restricted syndromes) should be included in different stratification strata at entry in RCT.

**References**


2-2 Which diagnostic criteria must be recommended for inclusion?

**Background**

Currently clinical trial eligibility is based on the degree of diagnostic certainty as defined by the El Escorial/Airlie House/Awaji criteria (EVID). Prior to 2010, trials restricted enrolment to subjects meeting criteria for definite, probable, or laboratory probable ALS. The recent inclusion of possible ALS as being equivalent to definite ALS has not led to any loss of specificity. ALS is now recognized to be a heterogeneous clinical condition with variable presentation and clinical progression.

A range of prognostic factors have been identified including genetic status (pathological hexanucleotide repeat expansions of C9orf72), slope of ALSFRS from the time of first presentation to diagnosis; site of onset; and the presence of specific domains of neuropsychological dysfunction. Differences in disease progression can affect outcome of clinical trials, as can the impact that neuropsychological deficits have on patient survival. Moreover, genetic and biologic profiles may also correlate directly with treatment response. Validated staging systems of prognostic utility have recently been developed (King’s and MiToS) that can assist in predicting outcome at the time of trial enrolment.

**Rationale 2-2-1:**

ALS is heterogeneous (EVID) and revised diagnostic criteria for trial inclusion are required (PRIN). Some forms of ALS have a genetic basis (EVID) that could affect the outcome of clinical trials (PRIN). Based on heterogeneity of disease pathobiology and disease progression, pre-specified enrolment criteria are necessary (INFER).

**Recommendation 2-2-1:**

Clinical trialists should include patients with clinically definite ALS, clinically probable ALS, probable ALS - laboratory supported, and clinically possible ALS, pending adjustment of the WFN diagnostic criteria. Also, clinical trialists should enroll sporadic and familial patients, unless otherwise pre-specified. DNA should be stored on all patients included in clinical trials.

**Recommendation 2-2-2:**
In recognition of the heterogeneity of ALS, clinical trialists must specify enrollment criteria based on their specific trial goals.

References:


2-3. Which factors require stratification – Riluzole use, study center, genetic etiology, predicted prognosis, presence of cognitive/behavioral dysfunction, etc.?

Background:

It is common for randomized trials to use a constrained allocation procedure in order to improve the balance of the treatment groups. The most commonly used methods are stratified block randomization and minimization, both of which constrain the allocation to ensure the characteristics of the treatment arms are similar with regards to some pre-defined characteristics of known prognostic importance. These characteristics are referred to as stratification factors. Stratification should not be confused with post-hoc subgroup analyses, which assess whether the effect of the treatment differs according to patient characteristics at entry into the trial.

In ALS there are multiple factors that impact phenotype and survival such as riluzole use, age of onset, site of onset, time to diagnosis, genetics (amongst others, C9orf72, UNC13a, SOD1 (A4V, D90A, etc.), ATXN2, FUS), co-morbid FTD, executive dysfunction and vital capacity. Although it is desirable to stratify for all of these factors, from a practical point of view it is simply not possible. In clinical trials stratification can realistically be performed for only 3 or 4 factors, depending on the size of the trial. These issue of having to stratify for too many variables could be overcome by the use of a reliable prediction model of prognosis if available.

Our knowledge of the underlying pathophysiology of ALS is increasing very rapidly. This new knowledge is also leading to different types of trials, such as gene-targeted trials, pathway-
specific trials, in addition to disease modifying and symptomatic trials. In gene-targeted trials the issue of genetic modifiers of survival are dealt with in the inclusion criteria, and investigators might want to stratify for C9orf72 repeat expansions in a large phase 3 trial. Depending on the trial design and outcome measures, different factors may require stratification, and there is no “one size fits all”.

Considering the heterogeneity of ALS, there is increasing interest in identifying subgroups of patients that show response to treatment in cases where the overall trial result was negative. Although subgroups of responders may exist, one should also consider the possibility that the “frequency of “responders” is due to an unequal distribution of prognostic factors within different groups.

**Rationale 2-3:**

Multiple factors (such as genetics, age and site of onset, etc.) influence phenotype and survival in ALS (EVID). In clinical trials stratification can only be performed for 3 or 4 factors (PRIN) and therefore stratification cannot be performed for all factors that modify phenotype and survival (INFER).

**Recommendations 2-3-1:**

Clinical trialists should choose for randomization those factors which are most relevant to the outcome measure of the trial. In large phase 3 trials the trialist should consider in particular stratifying for riluzole use, trial site and disease progression (as reflected in time to diagnosis from first symptoms, time from diagnosis to inclusion in the trial, or ALS-FRS-R slope prior to entry into trial).

**Recommendations 2-3-2:**

Clinical trialists should collect DNA from all participants to allow genetic post-hoc analyses

**Recommendations 2-3-3:**

Clinical trialists should perform post-hoc analyses in order to identify subgroups of patients which appear to respond better to treatment. Trialists must however interpret such analyses with caution since subgroups of responders may arise by chance, or may be an artifact caused by other prognostic factors.

**Recommendations 2-3-4:**

Clinical trialists should consider stratifying by predicted prognosis if reliable prediction models become available.

**References:**

SECTION 3. Outcome Measures

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3-1 Survival and functional outcomes

Background:

For a primary outcome in an ALS trial a reliable end point is needed in phase III clinical trials that is robust, reliably measured, and clinically meaningful. Disease duration measured as survival and functional scales fulfil these criteria.

Rationale 3-1-1

Premature death occurs in nearly all patients with ALS [PRIN]. Prolonging survival with improved function is of major interest in those with ALS [PRIN]. Numerous previous ALS trials have utilized survival as a primary outcome measure [PRIN]. More recently the ALSFRS-r has been validated and utilized in ALS clinical trials (Kaufman, 2005) [EVID]. Survival trials have the limitation of requiring large number of patients with a long follow-up time, while functional scales are limited due to deaths and variable follow-up periods with resulting missing data points (Messina, 2012) [EVID]. Those with the worst function in a clinical trial are most likely to die (Traynor, 2004; Kaufmann, 2005) [EVID] thus biasing the data [INFER].

Recommendation 3-1-1:

The investigator should include either a survival analysis or a functional assessment (such as the ALSFRS-r) as the primary outcome measure in a phase III ALS clinical trial with the alternative included as a secondary outcome.

Rationale 3-1-2:

The only participants left in clinical trials are those with good function, which may reduce the power to detect a moderate beneficial effect in the treatment arm since comparison is between two surviving groups, both with good function [INFER]. An attempt to adjust for these limitations is to perform an analysis with a combined approach to survival and function (Berry, 2013) [EVID]. The combined endpoint may provide enhanced power but does not convene a clinically meaningful outcome limiting the information that can be convened to patients on significance (Berry, 2013) [EVID].
Recommendation 3-1-2:

The investigator may include a combined survival/functional analysis as an exploratory endpoint in an ALS clinical trial.

3-2 Strength assessments

Background:

The cardinal symptom ALS patients report is that of progressive weakness. Thus accurate measurement of muscle strength represents a direct measure of disease status, and strength is directly related to function throughout the neuraxis. Because the FDA requires a clinically significant outcome for phase III clinical trials, assessment of strength offers an obvious choice for a primary outcome in ALS research. Strength testing however comes with data variability and requires a large number of patients for adequately powered studies. Quantitative muscle strength measures have been employed in multiple recent ALS trials (Cudkowicz et al 2013, 2014; Shefner et al. 2013); with rigorous training and validation, quantitative strength measurement has proven to be reliable and sensitive to change even in short duration clinical trials (Shefner et al. 2013).

Rationale 3-2-1:

Progressive weakness is a core symptom of ALS [PRIN]. Measurement of strength in ALS clinical trials has been shown to be reliable and valid while with some variability (GLALS, 2003) [EVID]. Strength has been measured both qualitatively and quantitatively in ALS trials; while quantitative measurement of multiple muscles can be averaged into a reliably measured value (GLALS, 2003), qualitative measurement is inherently nonlinear, and insensitive to modest changes in muscle strength (van der Ploeg, 1984) [EVID]. The power of a study is dependent upon the variability of the primary outcome measure [PRIN]. The variability of qualitative strength measurements lead to large numbers of patients for ALS trials when strength is used as a primary outcome measure [INFER].

Recommendation 3-2-1:

The investigator may include quantitative strength assessments as the primary outcome measure in any ALS clinical trial.

3-3 Quality of life measures

Background:

By its very nature, QOL is an important part of human existence, but it has been unclear as to the best way to apply it to disease. Many variables contribute to quality of life beyond the direct effects of ALS. There are many disease specific questionnaires, and ALS specific QOL measures have been validated (Lou, 2010; Simmons, 2015).

Rationale 3-3-1:

In a progressive, fatal disease such as ALS, accurately assessing QOL is an important care goal [PRIN]. ALS specific QOL tools have been developed and validated (Lou, 2010; Simmons, 2015) [EVID]. For these reasons, quantitative measurements of QOL are available for ALS trials [INFER]. Many factors impact the QOL scores on these scales besides the
pathophysiology of ALS [PRIN]. Therefore QOL scores alone do not provide compelling clinical evidence of a change in the pathophysiology of ALS and conclusions about change in disease progression cannot be inferred [INFER]. These QOL scales do however provide important insight into the impact the disease and disease treatments have on patients’ life satisfaction. Therefore, health-independent QOL scores may be included in ALS clinical trials as a secondary outcome measure to assess the impact of ALS and the intervention’s effect on personal life satisfaction. [INFER].

**Recommendation 3-3-1:**

Investigators may use health-independent ALS specific QOL scales as a secondary outcome measure.

**Rationale 3-3-2:**

There may be unique circumstances in symptomatic management trials, determined by the trial objectives, that a QOL scale could be used as a primary outcome [INFER].

**Recommendation 3-3-2:**

In symptomatic management trials, a health-independent ALS specific QOL scale may be used as a primary outcome measure.

3-4 Cognitive function

**Background:**

It has become increasingly recognized in the past decade that the biological effects of ALS are neurologically more diffuse than simply the motor weakness that has been appreciated since the original description of ALS.

While the motor manifestations of progressive weakness leading to death are the primary manifestation in most patients, many patients are now recognized with debilitating cognitive and behavioral problems (Strong 2009).

Historically ALS clinical trials have focused almost exclusively on the motor manifestations of the disease with little attention to the cognitive and behavioral manifestations of this disease. Good quantitative outcome measures exist for the motor manifestations (strength testing and survival) and for cognitive impairment (screening with ALS-CBS and more detailed analysis by neuropsychometric testing) (Murphy, 2016; Niven 2015; Wooley, 2010). However no such validated outcome measure exists for the behavioral deficits that develop in a minority of cases with ALS.

**Rationale 3-4-1:**

While the motor manifestations of ALS remain the primary source of morbidity and mortality for most patients [PRIN], smaller populations of ALS patients have debilitating cognitive and behavioral effects as well (Murphy, 2016) [EVID].

Management of ALS should include strategies to address these cognitive and behavioral manifestations in addition to the motor manifestations [INFER]. Therefore it is relevant and important to observe and measure these cognitive and behavioral outcomes in disease
modifying clinical trial of ALS [INFER]. As these are clinically relevant outcomes [PRIN], they may fulfil the FDAs requirements for a primary outcome in experimental treatments whose biological effects are hypothesized to impact cognitive function [INFER].

A number of quantitative instruments for cognition (but not behavior) have been developed that are now specifically validated in ALS to detect and quantify the cognitive impairment in ALS (Niven, 2015; Wooley, 2010) [EVID].

How the data from these cognitive tests may be applied to clinical trials is still unknown [PRIN]. The variability in the data (Niven, 2015; Wooley, 2010) [EVID] suggest large number of ALS subjects would be required for an adequately powered study [INFER].

**Recommendation 3-4-1:**

The investigator may include assessments of cognition function using validated instruments in ALS clinical trials as a primary or secondary outcome measure in clinical trials directed at treated cognition.

### 3-5 Pulmonary function

**Background:**

Respiratory failure via hypoventilation is the most common cause of death in ALS and respiratory failure carries a poor prognosis. Moreover maintenance of respiratory function has been associated with maintenance of both quality-of-life and survival (Bourke et al, 2006). Respiratory function therefore is an important candidate outcome measure for ALS. Measures of respiratory hypoventilation include: (1) symptoms (e.g. disturbed sleep, orthopnea); (2) volitional respiratory function tests such as FVC and sniff nasal inspiratory pressure (SNIP); (3) measurements of respiratory gases (O2 and CO2) either analysis of arterial blood or transcutaneously; and (4) direct measurements of diaphragm structure and function such as ultrasound. Symptomatic monitoring of respiratory function carries the disadvantage that it is subjective.

**Rationale 3-5-1:**

Reliable measurements of pulmonary strength and function are important disease milestones for ALS patients [PRIN]. Forced vital capacity (FVC) is significantly correlated with prognosis in ALS e.g. a study of 1034 patients showed that median survival of patients with baseline FVC <75% was 2.91 years compared to 4.08 years for baseline FVC>75% (Czaplinski et al, 2006) [EVID]. However volitional measures, such as FVC, are often confounded in patients with severe bulbar weakness and otherwise early stage disease [EVID]. Other methods of measuring ALS have been utilized as well, such as SNIP, transcutaneous oximetry and overnight oximetry O2 saturations, ultrasonic measures of diaphragm movement (Capozzo et al, 2014; Bach et. Al, 2004; Pinto et. Al, 2015) [EVID]. Thus far none have demonstrated clear superiority in ALS trials [EVID].

**Recommendation 3-5-1**

The investigator should use measures of pulmonary function as an outcome in ALS trials and these may be used as a primary outcome.
3-6 Electrophysiology

**Background:**

Electrophysiology can assess the function of the upper and lower motor neuron. In the diagnosis of ALS it is employed as an extension of, and in conjunction with the clinical examination. It is of proven value in, pre-clinical detection of ALS, confirmation of diagnosis in the correct clinical setting, substantiating upper motor neuron (UMN) deficit when clinically uncertain, and giving some qualitative measure of severity of disease. A variety of techniques have been used. Some are simple and well standardized, but others are more sophisticated, complex and unlikely to be universally applicable.

**Rationale 3-6-1:**

The pathophysiology of ALS is that of progressive loss of the cortical (upper) and spinal and bulbar (lower) motor neurons [PRIN]. Electrophysiology can provide an assessment of the spinal motor neuron function and central cortical conduction times [PRIN]. Electrophysiology measurements are valuable in ALS trials as a measurement of spinal motor neurons and more limited assessment of the cortical motor neurons [INFER].

Thus far techniques in ALS include using motor unit estimates (MUNE) [EVID] (Shefner, 2011) and motor unit number index (MUNIX) (Nandedkar, 2011; Neuwirth, 2011) [EVID]. These tests are limited by the number and type of muscles that can be tested though MUNIX can be applied more broadly than MUNE (Shefner 2011; Nandedkar, 2011; Neurwirth 2011) [EVID]. ALS does not affect all skeletal muscles equally in all patients [PRIN]. Extrapolating from individual muscles tested may not reflect the global disease burden in patients with ALS [INFER].

Additionally, electrophysiology measures do not provide direct clinical relevant information on ALS disease impact [PRIN]. The FDA requires demonstrating reproducible clinical improvement for consideration of a new drug for approval [PRIN]. Therefore electrophysiology would not be appropriate as a primary outcome for a phase III clinical trial [INFER].

Therefore electrophysiology represents a poor primary outcome measure in phase III clinical trials but does provide important supportive evidence on disease modifying effects [INFER].

**Recommendation 3-6-1:**

The investigator may use electrophysiology measures (such as MUNE or MUNIX) as a secondary outcome measure for ALS clinical trial.

**Rationale 3-6-2:**

Electrical impedance myography (EIM) is an electrophysiological method which allows for quantification of surface voltage and impedance in skeletal muscles upon application of high-frequency, low-amplitude electric current to the skin overlying a muscle (Ogunnika, 2010) [EVID]. It has already been applied in longitudinal assessments of ALS patients as a disease progression marker (Rutkove, 2014) [EVID].

EIM has been assessed in a variety of neuromuscular diseases such as radiculopathies, inflammatory and dystrophic myopathies (Ogunnika) [EVID]. Single – and multi-center studies in ALS patients suggest that EIM is a reliable and valid measure that correlates with ALS progression and other outcomes measures such as ALSFRS and hand-held dynamometry (Rutkove., 2014) [EVID]. Portable devices have been developed as well as an array for the
assessment of bulbar dysfunction, and first proof-of-principle reports have been published (Ogunnika et al., 2010; McIlduff et al., 2015) [EVID]. While these measures have demonstrated the potential value of EIM as an outcome measure in ALS clinical trials, it has not yet been validated as a global assessment of disease severity nor does it represent a direct assessment of a clinical function precluding its use as a primary outcome measure in phase III clinical trials [INFER].

**Recommendation 3-6-2:**
The investigator may use EIM as a secondary outcome in ALS clinical trials.

### 3-7 Bulbar scales

**Background:**
Bulbar onset has been estimated to occur in approximately 25% of all ALS patients. The primary pathological process contributing to morbidity and mortality in ALS involves bulbar dysfunction. This includes aspiration with tracheostomy, dysphagia induced weight loss, dehydration, and early PEG placement. Unfortunately, bulbar scales and measures have not traditionally been employed in ALS clinical trial design. Subsequently, valid information related to the clinical efficacy of trial drugs on bulbar function remains unknown. Consensus guidelines established for ALS clinical trial design in 1999 suggested the use of validated scales, although precise measurement of bulbar function had yet to be developed (Miller, 1999). Since these guidelines were established, validated scales for speech (speaking rate) (Ball, 2002), pseudobulbar affect (CNS-LS), and more recently bulbar function (BFS) have been developed. Speech system (sentence intelligibility, speaking rate) and speech subsystem (phonatory, resonatory, articulatory and respiratory) analyses have been successfully established for ALS. Protocols have subsequently been studied to assess bulbar dysfunction, articulatory constraints and speech deterioration, and the timing for speech intervention. Swallowing measures including MBS, FEES, PAS, and tongue EIM have also been studied as valid measures of assessing dysphagia over time. An increased incidence in bulbar onset has also been identified in several familial forms of ALS (Xiaowei, 2014).

**Rationale 3-7-1:**
Valid bulbar function scales now exist allowing investigators to critically follow patients with ALS throughout their clinical course (EVID). Bulbar dysfunction significantly contributes to death and disability with this disease (PRIN). Thus, clinical ALS trial design should include bulbar function scale, ALSFRS-R subscale analysis and/or functional measures, to effectively evaluate the efficacy of a candidate drug within the bulbar domain (INFER).

**Recommendation 3-7-1:**
The investigator should utilize available bulbar assessment scales or functional measures as secondary outcomes for clinical drug trial design.

### 3-8 Staging

**Background:**
ALS is a progressive condition in which the impact of disease on symptoms, function, and quality of life varies as disability increases, with resulting differences in treatment efficacy (Brooks, 1999), dependence on health services, and health economic costs.
Rationale 3-8-1:

Various methods of clinically staging ALS have been proposed (Hillel, 1989;; Roche, 2012; Chio, 2015) and partially validated (Balendra, 2015; Tramecere, 2015) [EVID]. Disease modifying therapies are more likely to be beneficial when the disease process is at an early stage [PRIN]. Therapies acting on function can only be effective when the relevant function is impaired (for example, non-invasive ventilation for neuromuscular respiratory failure) [PRIN]. Treatment efficacy therefore depends on the disease stage at which therapy is administered [INFER]. Maintaining disease at or reversing disease to an earlier stage is a desirable outcome [PRIN], and also has cost implications (Jones, 2014; Oh, 2015) [EVID].

Recommendation 3-8-1:

The investigator may include clinical stage as a secondary outcome measure in clinical trials.

3-9 Responder analyses

Background:

There has been an increased interest in responder analyses in recent years as our understanding of ALS as a multifactorial disorder has increased. This has arisen from the concern that a beneficial effect of a proposed treatment on a small subset of ALS cases with a shared unique pathophysiology may be missed in the broader analysis that includes all ALS cases in a clinical trial. Typically responder analyses include identifying ALS cases that progress more slowly than expected during a clinical trial and analyzing them in relationship to the remaining cases to identify unique or predictive variables (3). Responder analysis can also be used to compare numbers of responding patients in treated vs. controls (2). In this case, the definition of a responder is based on predetermined criterion, e.g. decline in ALSFRS-r score less than a pre-specified value (Beghi, 2013; Miller, 2015).

Rationale 3-9-1

There is a diversity of genetic causes for familial ALS and the mixed risk factors for sporadic ALS [PRIN]. There are multiple unique molecular pathways that lead to the same clinical phenotype of ALS [EVID]. It is likely that each of these molecular pathways responds to pharmacological intervention differently [EVID]. As a result it is likely that an effective treatment in a population with a shared pathophysiology may not be effective in the others [INFER]. Discriminating these unique populations provides the opportunity to test the efficacy in a more discrete manner [INFER]. Limitations at this time include a relative lack of understanding of the pathophysiology in most sporadic and a minority of familial ALS cases [EVID]. This precludes classifying each case of ALS by a specific pathophysiology [INFER]. As a result responder analyses are post-hoc with a retrospective review of baseline and observed variables [INFER]. Hypothesis confirmation requires a pre-specified hypothesis [PRIN]. Post hoc analyses do not have associated pre-specified hypotheses [INFER]. Therefore responder analyses can only be used as hypothesis generating and not hypothesis confirming [INFER]. Any hypothesis generated by responder analyses requires a prospective hypothesis driven clinical study for confirmation [INFER].

Recommendation 3-9-1:
The investigator may include responder analyses in their analysis of ALS clinical trial data, but these should be presented as hypothesis generating, rather than hypothesis confirming.

3-10 Technology assisted outcomes

**Background:**

Mobility in ALS patients gradually decreases with disease progression, due to a combination of increasing muscle weakness, spasticity and respiratory dysfunction. Technology-guided measurements of mobility such as use of pedometers, accelerometers, activity trackers and motion analysis systems can be used to more objectively quantify locomotor activities on a daily basis in comparison to patient-reported outcome measures.

**Rationale 3-10-1:**

Measurements of daily physical activity (ranging from light to vigorous intensity) by pedometers and other wearable devices or motion analysis systems have been mostly applied to healthy adults and children in prospective studies in order to analyze the impact of physical activity on general health or in sports, rehabilitation and occupational medicine (Vanroy et al., 2014; Ertzgaard et al., 2015) [EVID]. Because of the progressive weakness that occurs in ALS, patients become progressive immobilized [PRIN]. The ability to reliably quantitate and track physical activity in ALS subjects would be desirable [PRIN]. One pilot-study has assessed keyboard-typing activity in 19 ALS patients using an accelerometer as a marker of upper -limb dysfunction (Londral et al., 2015) [EVID]. However there is little experience with these devices with other physical activities in ALS [PRIN]. There are no studies published to date to determine how this type of data would perform under the rigors of an ALS clinical trial [INFER].

**Recommendation 3-10-1:**

The investigator may use technology-assisted measurements as an exploratory measure in ALS clinical trials.

3-11 Caregiver Measurements as Clinical Trial Outcome Measures

**Background:**

Several multi-national observational studies have indicated that caregiver-burden assessed by different clinimetric scales identifies an increasing burden for the patient caregiver dyad that might serve as an outcome for clinical trials if there is a beneficial treatment effect on the patient

**Rationale 3-11-1:**

Other neurodegenerative states have included direct or indirect caregiver information as outcome measures for clinical trials.

**Recommendation 3-11-1:**

The investigator may employ caregiver measurements as secondary endpoint in clinical trials unless there is a well-developed and evidence-supported justification for the use of such measures as primary endpoints.

3-12 Data quality

**Background:**
The outcome measures of some prior ALS studies have been difficult to interpret due to incomplete data from study drop-outs, missing data and increased data variability. Several ALS clinical trials have established multicenter networks establishing quality control for ALS-specific and normal control computerized isometric muscle strength measurements, manual muscle strength measurements, and hand-held myometry. In addition, comparable international quality control networks were established for pulmonary function test measurements.

Rationale 3-12-1:
Measurements of most outcome variables in ALS require some observation by study staff [PRIN]. ALS studies require more subjects than possible at a single site [PRIN]. Therefore multiple individuals across multiple sites will be making the same measurements [INFER]. To maximize value of the variable all examiners should perform the examinations in a uniform manner [INFER].

Recommendation 3-12-1:
All study examiners must undergo training to ensure they are obtaining uniformity of study procedures across sites and across time.

References:


32. Simmons Z. Patient-Perceived Outcomes and Quality of Life in ALS. Neurotherapeutics. 2015, 12:394-402.


SECTION 4. Therapeutic / Symptomatic Interventions in Clinical Trials

Participants

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4-1. Impact of Symptomatic Therapies and Supplements on ALS/MND Trial Outcomes

Background:

Symptomatic interventions are those that do not modify the underlying pathophysiology of ALS but impact specific symptoms and can indirectly affect the disease course. Management of symptoms may impact validated disease scales and survival outcomes, and alter trial outcomes. Some clinics initiate NIV and gastrostomy at diagnosis, while others intervene when the patient is more overtly symptomatic. Therefore these interventions will be quite variable as measures of function. A number of key symptomatic therapies warrant specific attention:

- Noninvasive ventilation (NIV): A randomized controlled trial of NIV demonstrated a significantly improved quality of life and provided a median survival benefit of 205 days [1].
- Nutrition and gastrostomy: i) A decrease in BMI is associated with faster rate of disease progression [2]. ii) A greater BMI at baseline is associated with longer survival [3]. iii) Enteral feeding is effective in increasing and/or stabilizing weight and BMI.
- Supplements: Persons with ALS often take supplements in an attempt to treat their disease process. The frequency of use, undocumented and variable efficacy result in a potential for a confounding effect in ALS/MND trials.

Rational 4-1-1:

Symptomatic treatments are a key component of care for individuals with ALS and can significantly impact the disease course (EVID).

Recommendations 4-1-1:

a. When a symptomatic intervention is effective (e.g. NIV), the investigator should consider its use for trial participants. Ethical implications and challenges to enrollment should be carefully considered if such a symptomatic intervention is used as an exclusion factor for participation.

b. Sponsors may exclude participants from a clinical trial if the bioavailability or mechanism of action of an investigational compound is affected by the presence and/or use of a symptomatic intervention (e.g. NIV or gastrostomy), but should not use the presence or
absence of an intervention (e.g. NIV or gastrostomy) as a proxy for function (e.g. low FVC or inability to swallow).

**Rational 4-1-2:**

Particular symptomatic therapies (e.g. NIV and nutrition support) are known to influence survival and/or quality of life [EVID] [1]. Differing use across trial arms (e.g. with regard to time initiated, type of NIV, usage by patient, effectiveness of ventilation), of symptomatic interventions will have an impact on survival and quality of life outcomes [INFER].

**Recommendations 4-1-2:**

a. Investigators should plan an *a priori* analysis of symptomatic interventions known to affect disease course (e.g. NIV implementation, gastrostomy placement).
b. Investigators should standardize and record use of interventions known to affect disease course within a clinical trial (e.g. NIV implementation, gastrostomy placement).
c. Investigators should record and analyze compliance with interventions known to affect disease course.

**Supplements**

**Rationale 4-1-3:**

There is insufficient evidence to state if the majority of supplements are either helpful, harmful or of no benefit in the setting of ALS.

**Recommendation 4-1-3:**

Investigators should discourage patients from taking supplements for the purpose of treating ALS when the potential interactions with the study drug are unknown.

**4-2. Conducting trials of symptomatic interventions in ALS/MND**

**Background:**

Symptomatic interventions are those that do not modify the underlying pathophysiology of ALS but impact on specific consequences of ALS. Symptomatic interventions may affect the disease course and prolong survival (e.g. NIV). Relatively few studies of symptomatic therapies have been completed.

**Rationale 4-2-1:**

Symptoms are a subjective experience of the individual suffering them and no “objective” measure is closer to the experience of the person [PRIN]. Patient reported outcome measures are useful to examine symptomatic therapies. [INFER]

**Recommendation 4-2-1:**

Trialists should utilize a patient reported outcome measure as either a primary or secondary outcome in trials intended to treat a specific symptom (e.g. muscle cramps, shortness of breath).
**Rationale 4-2-2:**

Trials of symptomatic therapies need to be conducted with rigorous methodology [PRIN]. Trial characteristics that improve methodological rigor include inclusion of a control group, randomization to treatment groups and masked outcome assessment (PRIN). Randomized crossover trials can also be utilized efficiently adding statistical power to smaller trials [EVID].

**Recommendation 4-2-2:**

Investigators should conduct rigorous randomized controlled trials of symptomatic therapies.

**Rationale 4-2-3:**

For symptom treatments with a generally accepted standard of care placebo controlled trials may be challenging or even unethical [PRIN].

**Recommendation 4-2-3:**

The investigator should employ standard of care comparative effectiveness and non-inferiority designed trials, assessing symptoms for which effective treatments are available (NIV, gastrostomy, etc.).

**Rationale 4-2-4:**

Medical devices can have a major impact, positive or negative, on survival and quality of life [EVID][1]. Current regulatory approval of medical devices is not the same as that for medicines, requiring a lower standard of evidence [EVID]. This can hamper development of the evidence base with high quality studies [INFER].

**Recommendation 4-2-4:**

The investigator or sponsor should evaluate interventional devices for efficacy and safety using studies with an RCT design.

**Rationale 4-2-5:**

Instruments measuring quality of life complement the conventional disease-related outcome measures in randomized trials. They reflect the influence of the disease on a person’s perception of physical health, psychological state, level of independence, social relationships, and personal beliefs [PRIN].

**Recommendation 4-2-5:**

The investigator should use quality of life measures in addition to conventional outcome measures in order to provide a more comprehensive assessment of treatment effects.

4-3. Multi-drug trials in ALS/MND

**Background:**
ALS is the result of a complex pathological cascade involving multiple cell types and parallel mechanisms converging to result in motor neuron cell death [4]. Thus, novel therapies could be aimed at multiple aspects of this disease cascade rather than a single aspect. Research efforts in other disease states have utilized combination drug therapies in which the involved agents have not shown individual efficacy (e.g. HIV, lymphoma), suggesting that single drugs used in combination ALS trials may not need to be separately efficacious, prior to use in multidrug trials.

**Rationale 4-3-1:**

Multiple pathological processes have been identified in ALS, but their relative contribution to disease progression and interactions remains uncertain [EVID]. Therefore, it is unclear if one drug can have a large clinical effect. A combination of drugs may be considered [INFER].

**Recommendation 4-3-1:**

Clinical trialists may consider multi drug therapy in ALS clinical trial design as candidate drugs become available.

**Rationale 4-3-2:**

If a combination of drugs with unknown activity in ALS proves efficacious, disease specific biomarkers relative to the various mechanisms being tested [PRIN] will be needed to assess the contribution of each drug[EVID][5].

**Recommendation 4-3-2:**

Trialists should measure disease specific assays for any combination drug trial to assess both clinical efficacy and the individual pathophysiologic mechanisms under evaluation.

**References:**

SECTION 5. Patient Recruitment and Retention

Participants

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5-1. Patient Perspective on Clinical Trials in General and on Trial Design

Background:
Clinical trials require the enthusiasm of patients and caregivers to support enrollment, minimize missing data, and avoid dropout. However, the burden of procedures in trials is increasing and recruitment is becoming more difficult (1). If ALS patients don’t perceive trials as fair and patient-centric they may decline to enroll, drop out early, or even attempt to unblind themselves (2). Leading clinical trial groups outside of ALS are increasingly partnering with patients and caregivers on protocols, recruitment, committees, and publications (3,4).

Rational 5-1-1:
ALS trials contain complex terminology and potentially burdensome study procedures which could be explained better (5) [EVID]. The number of procedures and tests in Phase III trials has been increasing by ~9% each year (1) [EVID]. More procedures lead to more burdensome trials for patients and caregivers [INFER]. In a survey of patients with ALS, 3 of the top 5 reasons for turning down a study were concerns about burdens (5) [EVID]. Patients have helped trial designers simplify trials and improve adherence. (6,7) [EVID]. Recruitment materials have been effective in other diseases (3,4,8,9) [EVID].

Recommendation 5-1-1:
Investigators should enlist patients and caregivers to develop simple recruitment materials and reduce the burden on patients.

Rationale 5-1-2:
Some patients choose not to participate because they are concerned about out of pocket costs (5)[EVID]. Even when these will be reimbursed by the trial, this policy is not always
communicated clearly, may not cover all expenses (e.g. babysitting, caregiver time off), and may have administrative delays [PRIN]. An expenses policy developed with patients, covering all relevant expenses, and paid promptly, may improve trial recruitment and retention [INFER]. Disease progression, travel difficulties, and caregiver burden represent common reasons for trial attrition (10) [EVID]. Among the possible interventions to reduce or compensate for study burdens, 3 out of 3 studies in other fields showed that payment for participation increased enrollment (11-14) [EVID].

**Recommendation 5-1-2**

a. Investigators should ensure that patients and caregivers are involved in developing the trial’s expenses policy and helping this be communicated clearly.

b. Sponsors should ensure adequate funds are set aside to fully offset patients’ out of pocket costs.

c. Investigators should ensure that patients and caregivers are offered appropriate levels of support to attend study visits (e.g. transport service, paid caregiver) and, if possible, to allow satellite clinic assessments, home visits, phone calls, or telemonitoring.

**Rationale 5-1-3:**

Patients and caregivers give up a great deal of time, energy, and effort to participate in a clinical trial [PRIN]. Despite this, they are rarely acknowledged formally in research articles (15) [EVID].

**Recommendation 5-1-3:**

The investigators must thank patients and their caregivers who took part in the trial (e.g. in the acknowledgements of articles and presentations arising).

**Rationale 5-1-4:**

Closing out the trial in a manner that does not meet patient’s expectations with regards to individual and group level feedback, group unblinding, medication tapering, and safety follow-up is likely to negatively affect patients’ interest in future trial participation (16) [EVID].

**Recommendation 5-1-4:**

Investigators should establish procedures of trial close-out early in the planning phase so they form part of the operations manual before enrollment commences.

**Rationale 5-1-5:**

While most patients want a summary of trial results (16-18) few get one (19), often after a long delay (20) [EVID].

**Recommendation 5-1-5:**

a. Investigators must promptly provide all participants a lay summary of the trial results, both written and preferably face-to-face, unless they opt out.

b. This summary should conform to best communication practices from the literature.

**Rationale 5-1-6:**
Most trial participants are unable to attend scientific congresses to learn about the results of trials in which they participated [PRIN].

**Recommendation 5-1-6:**

Investigators and funders should ensure conference presentations announcing study results are, when possible, video recorded or live-streamed and shared online with invitations to watch the presentation provided to trial participants and/or their caregivers.

**Rationale 5-1-7:**

Most trial participants are unable to freely access peer-reviewed scientific journal articles [PRIN].

**Recommendation 5-1-7:**

Investigators must ensure ALS clinical trial results are published, and are published open access.

**Rationale 5-1-8:**

Only a small number of research studies have been conducted in ALS to investigate issues around trial recruitment and retention (2,5,9,21) [EVID]. The lack of a consistent framework to record reasons for trial dropout makes it more challenging to minimize attrition (9)[INFER].

**Recommendation 5-1-8:**

Investigators should develop a systematic method to document reasons for trial dropout and consistently report these in study publications.

**References 5.1:**


5-2 Steps to Maximize Patient Enthusiasm/Participation

Background:

Less than 10% of patients with ALS enroll in trials and the mean ALS trial enrollment rate is about 2 patients per site per month (1). While similar to other diseases (2-4), these numbers seem surprisingly low given the severity of ALS and the paucity of current treatment options. Consequences of such low enrollment include trials taking longer, being more costly, terminating prematurely without an answer, and difficulty generalizing trial results (5-7). Surveys suggest modifiable “patient factors” and “doctor factors” that contribute to low enrollment in ALS trials (1,8), similar to those found in other fields (9). The most common patient factors responsible for low enrollment are lack of awareness of trial options (8,10), burdens associated with participation (time, money and physical, 8) and confusion about research (8). A surprisingly common doctor factor responsible for low enrollment is failure to personally educate and advocate for ALS trial participation to one’s own patients (1).
Rationale 5-2-1:
A survey of patients with ALS suggested that most get their information about research studies from patient support and advocacy websites and from support groups (8) [EVID].

Recommendation 5-2-1:
Investigators should advertise newly opened trials on patient support and advocacy websites and in support groups.

Rationale 5-2-2:
In one well-conducted randomized trial, an advertising method that required patients to “opt out” was associated with significantly higher subsequent enrollment than one requiring patients to “opt in” to hear about a colorectal cancer screening study (9,11) [EVID].

Recommendation 5-2-2:
Investigators should use advertising methods that require patients to “opt out” (such as the National ALS Registry’s Research Notification Tool) rather than “opt in” to receive alerts about each new study.

Rationale 5-2-3:
Surveys suggest that many ALS patients are confused about trial specifics including rationale, design and physical and financial risks (8) [EVID]. Consent forms explain these but are inadequately understood by many trial participants (12) [EVID]. In some (but not all) studies in other fields, educational materials that supplement the consent form such as videos can improve understanding and boost enrollment (9,13,14) [EVID]. Some patients may attempt to unblind their trial allocation during a trial through use of social media (15)[EVID], or other means.

Recommendation 5-2-3:
  a. Site investigators should use supplemental educational materials such as videos or on-line webinars in the consenting process to increase participation in ALS trials and to enhance understanding of trial goals and limitations
  b. Investigators should partner with patients and caregivers to underscore the risk to research studies of patients unblinding themselves while enrolled in trials.

Rationale 5-2-4:
Among surveys of patients with other diseases who participated in trials, “physician influence” is usually one of the top reasons given for participation (16) [EVID]. A surprising number of ALS clinicians are not educating or advocating for enrollment to their patients (1) [EVID].

Recommendation 5-2-4:
Clinicians should educate and advocate for enrollment into clinical trials to their patients with ALS.
References 5.2


5-3 Expanded Access

Background:

Expanded Access programs (EAPs, in USA) or Compassionate Use programs (CUPs, in Europe) are mechanisms by which patients with incurable or life threatening conditions can gain access to unapproved drugs, biologics and medical devices if they are ineligible to participate in the clinical trials evaluating them. There is increasing pressure by patients and caregivers to obtain access to such treatments, including via the courts, because of the asserted right to take potentially life-saving or life-prolonging drugs before their approval by regulatory authorities. EAPs and CUPs are differently regulated by FDA, EMA, PMDA and other national regulatory authorities [EVID].
Rationale 5-3-1:
The majority of patients affected by ALS are excluded from participating in current clinical trials [EVID]. This increases the pressure of patients to be included in EAPs/CUPs [INFER].

Recommendation 5-3-1:
Investigators should reduce stringency of clinical trial protocols in order to gain more participants, without reducing the trial’s capacity to obtain scientifically valid data.

Rationale 5-3-2:
Large scale EAPs/CUPs could compromise patient enrollment and retention in clinical trials [PRIN].

Recommendation 5-3-2:

a. Investigators should harmonize the design and conduct of large scale EAPs/CUPs with research clinical trials using specified rules concerning enrollment criteria, dosage, and monitoring.

b. Investigators, companies, and regulatory authorities should conduct large scale EAPs/CUPs with the involvement of ALS centers where research clinical trials are performed and high quality data are collected.

Rationale 5-3-3:
Pharmaceutical and research companies and investigators are concerned that important safety and efficacy data will not be collected accurately or at all when patients participate in EAPs/CUPs and not in regulated clinical trials [PRIN]. Because EAP/CUP design requirements are less regulated than in registration trials, with the exception of the reporting of adverse events/serious adverse events [EVID], the collection of accurate clinical information useful for the patients and scientific community may be neglected [INFER].

Recommendation 5-3-3:
Providers should collect basic clinical and laboratory data with a standardized form to ensure an adequate level of safety as well as data uniformity and quality. Providers should share these data with appropriate parties (e.g. regulatory authorities).

Rationale 5-3-4:
The cost of participation in EAPs/CUPs is highly variable and often not supported by third parties (i.e. insurance companies, ALS patient organizations, and government agencies) [PRIN].

Recommendation 5-3-4:

a. Those designing EAPs/CUPs should allow for sponsor cost recovery but not for profit

b. Those designing EAPs/CUPs should explore the possible role of national and local organizations, insurance companies, and government agencies as payers.

Rationale 5-3-5:
Patients and caregivers try to procure experimental drugs and therapies by any means available with such discussions being widely shared within patient communities, blogs, and chat rooms [PRIN]. Although not confidential, this information is also not scientifically or expertly managed [INFER].

**Recommendation 5-3-5:**

Investigators should provide patients and caregivers information about experimental drugs and therapies, as well as unconventional therapeutic approaches advertised via social media.

**5-4 Right to Try**

**Background:**

Right-to-try legislation refers to laws stating the right of terminally ill patients to try experimental therapies (drugs, biologics, devices) that have passed Phase 1 testing but have not been approved for clinical use by the Food and Drug Administration (FDA) [EVID].

**Rationale 5-4-1:**

The Right to Try movement states that terminally ill patients have access to potentially effective drug treatments that have passed Phase 1 testing and are deemed safe [EVID].

**Recommendation 5-4-1**

Because experimental drug safety and efficacy are not definitively demonstrated in Phase 1 clinical trials, drug developers (e.g., pharmaceutical companies) should accelerate subsequent phase 2 trials during which more reliable data on these parameters are obtained.

**Rationale 5-4-2:**

ALS patients may ask their treating physicians to prescribe drugs that have not completed Phase 2 and Phase 3 clinical testing, because of right to try laws passed by several states [EVID].

**Recommendation 5-4-2:**

The treating physician should discuss with the patient the limits of these laws, including (1) inability to obtain a legally valid informed consent because the utility of a drug not tested for efficacy is unknown, (2) the requested drug cannot be considered a ‘therapy’, and (3) lack of financial provisions for paying the expenses of treatment.

**References 5-3 and 5-4:**

5. Food and Drug Administration. 21 CFR Parts 312 and 316

Revised #18 & #19 from “Consensus guidelines for the design and implementation of clinical trials" by Miller et al, J Neurol Sci 1999

18. An Independent Data and Safety Monitoring Committee (IDSMC) should be established for each trial. This should consist of independent physicians, at least one of whom is a recognized expert in ALS, and biostatisticians who periodically review all data during the conduct of the trial and at its conclusion. The members of the IDSMC should have access to all information concerning the safety and conduct of the trial. Other experts, such as an epidemiologist, would be desirable. This Committee issues advice on premature termination. It is also responsible for safeguarding against scientific fraud. It is essential that this committee be free of conflict of interest and act on the patient’s behalf.
19. A Steering Committee should be established by mutual agreement between the company and the investigators. It should include representatives selected by the investigators, the Sponsor, and outside experts if and when needed. Involvement of patient advocates (patients
living with ALS and their caregivers) is essential. This Committee is responsible for finalizing written agreements between investigators and Sponsor concerning:

- protocol
- general agreement guidelines
- consent form and information sheet
- full disclosure of all financial relationships between Investigator and Sponsor and other possible sources of conflict of interest
- patient indemnity
- open-label trials
- selection of members of the IDSMC
- release of information to the public before, during and after the trial
- arrangements for 'open label' extension of therapy if appropriate at the conclusion of the trial
SECTION 6. Biomarker Working Group

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6-1. How might biomarkers be useful in ALS clinical trials?

Background:

Despite a multitude of clinical trials, Riluzole is the only medication currently licensed for patients with amyotrophic lateral sclerosis (ALS). The reasons are many and complex, but a paucity of biomarkers has been identified as an important contributing factor. Biomarkers, defined as "characteristics that are objectively measured and evaluated as indicators of normal biological processes, pathological processes, or biological responses to therapeutic interventions", may facilitate greater success of ALS clinical trials. Various types of biomarkers are recognized (Table 1), each with a different potential application in the clinical trial setting. For the purpose of these guidelines we use the term “candidate biomarker” to refer to those measures which have the potential to be utilized for their intended function, but for which definitive evidence is still lacking.

Table 1 – Types of Biomarkers

<table>
<thead>
<tr>
<th>Type of Biomarker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic:</td>
<td>A diagnostic biomarker is a disease characteristic that categorizes a person by the presence or absence of a specific disease.</td>
</tr>
<tr>
<td>Prognostic:</td>
<td>A prognostic biomarker is a baseline characteristic that categorizes patients by risk of a disease or progression of a disease.</td>
</tr>
<tr>
<td>Predictive:</td>
<td>A predictive biomarker is a baseline characteristic that categorizes patients by their likelihood of response to a particular treatment.</td>
</tr>
<tr>
<td>Pharmacodynamic:</td>
<td>A pharmacodynamic biomarker is one for which a change in the biomarker shows that a biological response has occurred in a patient who has received a therapeutic intervention.</td>
</tr>
<tr>
<td>Disease Progression:</td>
<td>Absent from other lexicons on biomarkers, this term describes a biomarker that changes as disease advances.</td>
</tr>
</tbody>
</table>
**Rationale 6-1:**

ALS is an etiologically and biologically heterogeneous disease (EVID 1, 2) with the implication that all patients may not benefit to the same extent from the same therapeutic (PRIN). Tools that identify patients with shared etiology or biology may aid clinical trials by allowing identification of subsets of patients most likely to benefit from a particular experimental therapeutic that affects upstream biological mechanisms (rather than downstream mechanisms common to all causes of axonal neurodegeneration) (PRIN).

**Recommendation 6-1-1:**

In designing and implementing ALS clinical trials, investigators should incorporate predictive biomarkers as eligibility criteria, to define patient populations most likely to benefit from the therapeutic under investigation.

**Rationale 6-1-2:**

ALS is a phenotypically heterogeneous disease (EVID 3). This variability in the natural history of disease diminishes the power of a clinical trial to detect a therapeutic benefit (PRIN).

**Recommendation 6-1-2:**

In designing and implementing ALS clinical trials, investigators should incorporate prognostic biomarkers as eligibility or stratification criteria, to define subsets of patients in whom there is greater likelihood of demonstrating the effect of an experimental therapeutic.

**Rationale 6-1-3:**

The use of traditional clinical measures (e.g., survival, rate of decline of the revised ALS functional rating scale [ALSFRS-R]) of therapeutic efficacy requires large studies with prolonged follow-up (EVID 4). This limits the ability to rapidly evaluate experimental therapeutics in multiple dosages during the mid-phase (phase II) of drug development (PRIN). In turn, this undermines the ability to make optimal decisions about which drugs (and at which dosages) should advance into larger, longer-duration, multi-center clinical trials (PRIN). Furthermore, in the absence of appropriate biomarkers, the results of large negative phase III clinical trials are difficult to interpret insofar as they may not provide information about whether the drug reached its target or impacted the intended biological mechanism (PRIN).

**Recommendation 6-1-3:**

In designing and implementing ALS clinical trials, especially phase-II, investigators should incorporate candidate pharmacodynamic biomarkers with potential to demonstrate adequacy of drug delivery, target engagement, or biological activity of the experimental therapeutic.

### 6-2. What criteria should be used to identify the most promising biomarkers for ALS clinical trials?

**Background:**

The utility of biomarkers may differ depending on the stage of therapeutic development, with perhaps the greatest potential in mid-phase development. In phase II trials, for example, the major challenges are determining whether the experimental therapeutic has reached and
engaged its biological target, affected the intended biological mechanism, or slowed the neurodegenerative process. In considering the potential use of biomarkers to demonstrate such effects, a distinction should be made between generic biomarkers of motor neuron loss (e.g., neurofilament) and biomarkers that might be specific to a drug with a particular mechanism of action (e.g., inflammation). Since demonstrating engagement of a particular drug target or biological mechanism will be specific to each individual experimental therapeutic, here we consider the more general potential utility of biomarkers to provide evidence that the neurodegenerative process has been slowed. Moreover, the success and sound conclusion of any clinical trial depends on the quality of its experimental design, including the measurement procedures employed. Quality control programs are beneficial for longitudinal, multicentre and epidemiological studies.

Rationale 6-2-1:

A plethora of candidate biomarkers have emerged from intense discovery efforts, but few (if any) are ready for use in clinical trials to aid decisions about the advancement of experimental therapeutics through the drug development pipeline. This reflects, at least in part, the absence of defined quality criteria against which candidate biomarkers may be evaluated for their readiness for utilization in clinical trials (PRIN).

Recommendation 6-2-1:

Investigators must ensure that biomarkers are quantifiable; are measured using standardized operating procedures; and can be measured reliably across multiple centers, accounting for relevant sources of variability, including intra- and inter-subject, intra- and inter-assessment (assay, evaluator, scanner) and inter-laboratory/site.

Rationale 6-2-2:

While clinical information available at the time of trial enrollment (e.g., bulbar onset, latency from symptom onset to diagnosis) may be useful in predicting future prognosis, significant residual person-to-person heterogeneity in the rate of disease progression and in survival time remain.

Recommendation 6-2-2:

In developing prognostic biomarkers, investigators must demonstrate that these biomarkers yield estimates of prognosis that are more informative than those based on readily available clinical information.

Rationale 6-2-3:

The growing recognition that ALS represents a clinical syndrome, with multiple causes and potentially diverse underlying upstream biological mechanisms, provides a rationale for undertaking clinical trials in subsets of patient populations identified as being most likely to benefit from a particular experimental therapeutic (PRIN).

Recommendation 6-2-3:

In developing predictive biomarkers, investigators must demonstrate that the biomarker meaningfully informs the likelihood of a future response to treatment.
**Rationale 6-2-4:**

Measures of disease progression, for which the natural history is defined, may aid clinical trials by providing a benchmark against which the effect of an experimental therapeutic can be measured (PRIN). Clinical measures of function (e.g. ALSFRS-R, vital capacity) or muscle strength (e.g. manual muscle testing), measured longitudinally, serve as useful measures of disease progression (EVID 10), but trials using such measures typically require large numbers of patients to be followed over an extended period of time for adequate power (EVID 11). Biomarkers will be most useful for drug development if they permit quantification of disease progression in a smaller number of participants and over a shorter period of time than traditional clinical outcomes (PRIN).

**Recommendation 6-2-4:**

Investigators *must* demonstrate that a biomarker of disease progression changes longitudinally in a manner that is biologically plausible and improves power to demonstrate an effect over a shorter duration and/or with a smaller number of participants compared to the ALSFRS-R.

**Rationale 6-2-5:**

Biomarkers reflecting disease progression represent one potential type of pharmacodynamic biomarker. In addition, biomarkers that are quantifiably different in ALS patients compared to the healthy population, even if the levels of these biomarkers do not change over time in the untreated state, may serve as potential pharmacodynamic biomarkers of treatment effect insofar as normalization of the biomarker following treatment would provide evidence of the pharmacological effect of the therapeutic (PRIN). Pharmacodynamic biomarkers can only be validated once an effective therapeutic has been identified (PRIN).

**Recommendation 6-2-5:**

Investigators *must* demonstrate that a pharmacodynamic biomarker changes in response to administration of a treatment in a manner that is consistent with the intended biological effect.

**6-3. What is the current status of candidate biomarkers for advancing ALS therapy development?**

**Background:**

A plethora of biomarker candidates, including biological fluids, neuroimaging and neurophysiological studies, have emerged. To ensure that these candidates meet the minimum methodological criteria outlined above (see Question #2), will also require consideration of pragmatic issues such as patient tolerability, burden of participation, investigator time, cost, complexity, need for specialized equipment, training and certification (PRIN).

**Rationale 6-3-1:**

A distinction should be made between biomarker development and the use of biomarkers to support go-no-go decisions in clinical trials (PRIN). Most candidate biomarkers have not yet met the minimum methodological criteria and, as such, cannot yet be used in clinical trials to make go-no-go decisions (EVID 6).


**Recommendations 6-3-1:**

Investigators *must* accumulate additional experimental data in order to support the use of biomarkers in future clinical trials for go-no-go decisions.

**Rationale 6-3-2:**

Biomarker development can be aided by both positive and negative trials (PRIN).

**Recommendations 6-3-2:**

Investigators and sponsors *should* make candidate biomarker development an essential component of all clinical trials.

**References:**

SECTION 7. Different Trial Phases and Beyond

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7-1 What is the role of alternative designs (futility, etc.)?

**Background:**
As we improve our knowledge of ALS biology and novel therapeutic targets are uncovered, alternative study designs can provide an opportunity to more efficiently and rapidly conduct clinical trials to evaluate potential therapies.

Adaptive trials and dose-finding designs are now well accepted and can be efficient trial designs. For example, a biomarker adaptive trial allows for modifications based on short-term biomarkers. Adaptive randomization designs allow for modifying randomization schedules when assigning subjects to treatment groups. Seamless Phase II/III design combines the biomarker discovery, safety and tolerability evaluation with an efficacy study, saving the time of completing a phase, reviewing the data, and starting up the next phase of the trial. Enrichment designs implement screening or lead-in analysis to determine candidates most likely to benefit from treatment, thus reducing heterogeneity, and while criticism about biased effect estimates and lack of generalizability are important to bear in mind, enrichment may substantively reduce ALS heterogeneity. Futility designs can halt development of therapies based on lack of feasibility or recruitment, or for lack of efficacy, saving time and money.

**Rationale 7-1-1:**
Alternative study designs offer unique advantages that cannot be obtained using traditional designs in rare, heterogeneous diseases (EVD). At the same time, their use presents statistical complexity and requires careful evaluation by an entire study team.

**Recommendation 7-1-1:**
Investigators should work with biostatisticians to consider traditional and alternative designs, and choose the one that best suits the therapeutic stage of development, available biomarkers and outcome measures to most efficiently evaluate an investigational therapy.
7-2 What is the ideal phase II trial?

Background:

Phase II trials can assess optimal dosing, expand pharmacokinetics, determine if a therapy has the desired biological effect, monitor safety and tolerability and/or determine whether a potential therapy reaches and affects its intended target. Phase II studies are typically underpowered to fully assess survival differences. Clinical efficacy is not the main goal of a phase II study.

At the same time, the safety and preliminary efficacy data collected from a phase II trial will inform phase III trial design. Respiratory measures (e.g., forced vital capacity (FVC) or slow vital capacity (SVC)) are important, since ALS results in respiratory failure and death. Because ALS causes disability, it is desirable to use an accepted outcome measure that allows for remote collection of data (e.g., the Revised ALS Functional Rating Scale (ALSFRS-R)). At least one ALS-specific quality of life scale shows little decline with disease progression and are likely an insensitive measure.

Rationale 7-2-1:

Biological assays and biomarkers (See Section 6) are useful to inform whether an investigational therapy produces the desired biological effect and target engagement (EVD). In phase II trials, investigators should include candidate biomarkers, when available, to ensure target engagement, and expanded pharmacokinetic (PK) evaluations unless all appropriate PK has been completed.

Rationale 7-2-2:

Use of reproducible and quantitative measures of strength, respiration, or physical function with low intra-examiner and inter-examiner variability are important outcome measures in a clinical trial. Therefore, adequate training when measuring clinical outcomes is important (INF). Patient positioning, evaluation times, cost, and training are important considerations in choosing an outcome measure (EVD). Additionally, uniform assessment of drug safety and tolerability are critical to the collection of reliable information (PRIN).
Investigators must ensure that all evaluators have adequate training for assessments and safety monitoring.

**Rationale 7-2-3:**

While phase II ALS trials are not meant to establish efficacy\(^2,^3,^4\) (EVD), it is appropriate to include efficacy outcomes for a number of purposes.

**Recommendation 7-2-3:**

Investigators should include appropriate clinical outcome measures in phase II to optimize the choice of outcome measures for a phase III trial and to evaluate for any unintentional deleterious impact of the therapeutic on ALS progression.

**References:**


**7-3. How do we make decisions to move from phase II to phase III?**

**Background:**
Phase II trials are part of early drug development. Often referred to as the learning phase of drug development, these studies provide requisite information instrumental in the design of efficacy trials. They are not expected to definitively establish efficacy\(^1,2,3\), yet it is appropriate to include efficacy outcomes, and it may be possible to see preliminary efficacy in phase II trials.\(^4\)

The duration and sample size for a phase II study depends on the study goals, and more than one phase II study might be required for a clinical development program to move forward to a phase III trial.

**Rationale 7-3-1:**

Phase III trial design is based on an understanding of certain characteristics of the investigational therapy observed in phase II including safety, tolerability, optimal dose, target engagement, and biological effect (PRIN). Well-designed phase II trials provide critical information about dosing, safety, tolerability and target engagement of the intervention being tested, supporting rational phase III trial design (INF).

**Recommendation 7-3-1:**

Investigators may move from phase II to phase III with at least adequate information on safety and tolerability for further testing (ideally overseen by an independent safety monitor), and investigators should move forward if there is safety and tolerability in combination with 1) information regarding pharmacodynamically optimal dose and/or 2) evidence of target engagement.

**Rationale 7-3-2:**

It is important to prioritize development of biological assays to determine if the intervention produces the desired biological effect. (EVD)\(^3,5,6\) (See section 6) Phase II ALS trials are generally under-powered to detect clinical effect, yet when trial results do not demonstrate clinical efficacy, enthusiasm can be dampened. (INF) Novel methods for exploring preliminary efficacy in phase II trials might help give an early estimation of effect, and could include ideas such as the application of predictive algorithms or historical control arms. While not meant to supplant the phase III efficacy study, these methods could provide additional early evidence to bolster a decision to move to phase III trials.

**Recommendation 7-3-2:**

Investigators may assess biological effect and/or preliminary efficacy, even using novel methods (e.g. predictive algorithms or exploratory biomarkers), to support a decision to move a therapy forward to phase III trials.

**References:**


7-4 What is the ideal phase III trial?

Background:

Since the approval of riluzole, there have been two decades of clinical trials conducted in patients with amyotrophic lateral sclerosis (ALS) that resulted in either no beneficial effect or adverse effects of the tested drugs. Thus, there is an urgent need for new medications to treat ALS. The long track record of negative phase III trials has provided insight into the development strategy and clinical trial design of potential therapies for ALS.i1,2.

Rationale 7-4-1:

Preclinical evaluation, clinical pharmacology, translation into humans, biomarker evaluation and clinical trial design all have to be considered when developing a phase III clinical trial. 2, 3 (EVD) A multidisciplinary or cross-functional approach to the development of a new investigational therapy would increase the likelihood of success in phase III (INF). A panel of basic scientists, pharmacologists, investigators, patients and clinical experts may aid the development of an ideal phase III trial (INF).

Recommendation 7-4-1:

Investigators should obtain input from biostatisticians, patient advocates, basic scientists and clinical trial experts to evaluate the overall scientific basis of the trial and inform its design.

Rationale 7-4-2:

Lack of complete understanding of dose-response of an investigational therapy may lead to a failed phase III trial. 3 (EVD) Phase II studies can explore dose-response and support dosage selection for phase III trials (INF).

Recommendation 7-4-2:

Investigators should design phase III trials to adequately evaluate the dosage of the investigational therapy, based on dosing data from phase II. However, if dose-response is not known from early phase trials, investigators may evaluate multiple dosages.

Rationale 7-4-3:

Earlier phase trials evaluate the safety and tolerability of an investigational therapy whereas phase III trials aim to demonstrate clinical efficacy (PRIN). Although there are study designs that assess efficacy without the use of placebo controls, a randomized, placebo-controlled clinical trial is the most robust way to demonstrate efficacy of an intervention. 4

Recommendation 7-4-3:
Investigators should include a placebo-controlled comparator to assess efficacy in phase III trials.

**Rationale 7-4-4:**

Phase II trials provide an opportunity to evaluate preliminary signals of efficacy and can inform potential endpoints in the phase III trial.\(^5\) (EVD) When designing phase III trials, the sample size is based on the endpoint’s clinical meaningfulness, expected treatment benefit, and the power to detect such a difference. (PRIN)

**Recommendation 7-4-4:**

Investigators should carefully review the results of the phase II trials and choose a primary end point that is clinically meaningful and adequately powered for phase III.

**Rationale 7-4-5:**

Clinical trials that do not demonstrate therapeutic benefit are less likely to be published or cited.\(^6\) (EVD) This publication bias may prevent the scientific community from critically analyzing prevailing theories and potential new avenues of research. (PRIN)

**Recommendation 7-4-5:**

Investigators should publish all clinical trial results, negative or positive, so that it is available widely to the ALS community.

**References:**


**7-5: Are there special considerations for cell and gene therapies?**

**Background:**

The possibility of benefit from gene and stem cell therapies is real. Gene therapy strategies include antisense oligonucleotide administration and viral vector-associated delivery of DNA or RNA to alter trophic factor expression or alter gene expression or RNA transcription to prolong motor neuron survival. Stem cell therapies exert their effects by altering the environment around degenerating motor neurons. Preclinical animal studies have shown some beneficial effects of both of these therapeutic strategies on specific targets\(^1,2\). Preliminary safety in
patients has been shown with intrathecal SOD1 antisense oligonucleotides, intramuscular AAV-9 delivery of a transcriptional factor to upregulate VEGF, and stem cell implantation into the lumbar and cervical spinal cord. Many additional strategies are under intense investigation in the preclinical arena.

**Rationale 7-5-1:**

There are special challenges and opportunities in performing early phase gene and stem cell therapy trials in ALS, which require special approaches and unique trial designs for testing these therapies.

**Recommendation 7-5-1:**

Investigators should take novel approaches to trial design, as dictated by the intervention characteristics, to appropriately study gene and cell therapies with potentially invasive delivery or lifelong biological effects, such as designing trials to evaluate efficacy beginning with phase I trials.

**Rationale 7-5-2:**

Promising preclinical results can result from factors unrelated to a biological effect and only meticulous, thorough and well-designed preclinical programs will yield reliable preclinical results (EVID).

**Recommendation 7-5-2:**

Investigators must only select gene or stem cell therapies for testing in clinical trials after appropriate pre-clinical efficacy and safety testing.

**Rationale 7-5-3:**

Variables, such as vector type, delivery method, immunosuppression protocol, dose, cell type and gene size, require thorough examination in animals and humans to identify the optimal regimen for trials (PRIN).

**Recommendation 7-5-3:**

Investigators must specify the immunosuppression protocol (if one is used), the vector/stem cell delivery routes, dose, cell type and gene size and the rationale for the choices.

**Rationale 7-5-4:**

As these therapies can induce long-lasting changes in a host, plans to monitor their effect, toxicity, and durability are necessary (PRIN).

**Recommendation 7-5-4:**

Investigators of gene and cell therapies should develop a long-term monitoring plan to assess carcinogenesis, immune responses to vectors, protein products, survival of engrafted cells, off-target effects, and long-term efficacy.
Rationale 7-5-5:

Gene discovery is still in an early phase in ALS, and some therapies may be directed only at people with ALS in the setting of a particular genetic makeup (EVID). These populations can be genetically identified prior to trial enrollment.

Recommendation 7-5-5:

Investigators of gene therapy should study populations appropriate to the therapeutic mechanism of action. If investigators have a rationale for including participants beyond a genetically defined subpopulation they should clearly delineate this rationale.

Rationale 7-5-6:

Biomarkers, to examine whether there is a biological response to a therapeutic, are desperately needed in ALS trials, and may be both more available and critically important when a given gene is targeted. (PRIN)

Recommendation 7-5-6:

Investigators should include at least one biomarker to monitor target engagement (eg. SOD1 mRNA or protein levels in CSF, CSF C9RANT peptides).

Rationale 7-5-7:

Efficacy of gene and cell therapies is dependent upon changes in the motor neurons and/or surrounding cells, many of which are demonstrable on pathological examination. (PRIN)

Recommendation 7-5-7:

Investigators should encourage autopsy for cell and gene therapies with potentially life-long biological effect.

References:


Update on Recommendation #13 (published Miller et al 1999).

7-6: What are the principles of Phase I trial design in ALS?

Background:
The development of novel therapeutics, in particular the transition from pre-clinical studies to first-in-human (phase I) trials, involves the potential for substantial risk. The purpose of phase I studies is to define the acute safety profile, pharmacokinetic profile, and maximum tolerated dose of a therapeutic. Many times, phase I trials incorporate single ascending dose (SAD) and multiple ascending dose (MAD) designs to accomplish these goals. Phase I ALS trials have been done in healthy volunteers and people with ALS under different circumstances.

Rationale 7-6-1:
In general, first-in-human phase I trials in ALS include a single ascending dose (SAD) study to understand initial acute safety and pharmacokinetics, as well as to determine maximum tolerated dose. This is generally followed by a multiple ascending dose (MAD) study to evaluate the toxicity after multiple doses or longer exposure to the intervention (EVD).

Recommendation 7-6-1:
Investigators should use single and multiple ascending dose ALS trials to evaluate safety, pharmacokinetic (PK) profile, and maximum tolerated dose (MTD).

Rationale 7-6-2:
SAD and MAD studies can include a placebo comparator (PRIN), and in many cases investigators have been encouraged to include a placebo group. One of the major reasons to include a placebo group is to help evaluate whether observed adverse events are a result of the intervention, or events that occur randomly (for example, events affecting those receiving placebo and the intervention). However, in certain circumstances, the delivery of the study intervention is potentially harmful and the inclusion of a sham procedure may not be warranted (EVD).

Recommendation 7-6-2:
Investigators should include a placebo control in phase I ALS trials to evaluate adverse event rate in treatment and placebo groups, but may omit placebo when its inclusion involves excessive risk (eg. associated with delivery).

Rationale 7-6-3:
SAD and MAD studies of potential ALS interventions can be performed in ALS patients or healthy volunteers (PRIN). In most cases, involving healthy volunteers for these initial studies reduces risk, since healthy volunteers are more likely to be resilient to potential adverse events caused by a study intervention (INF). Furthermore, enrollment may be faster in healthy
volunteers. However, in some cases, the phase I trial involves biomarker assessment that can only be done in people with the disease, or the therapy could have some potential benefit in people with ALS, even at a single dose or short course of treatment\(^3\) (EVD), in which case a phase I trial might be done in people with ALS.

**Recommendation 7-6-3:**

Investigators should conduct phase I studies in healthy volunteers unless compelling reasons exist to include people with ALS.

**References:**

SECTION 8. Different Trial Phases and Beyond

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8-1. What lessons can we learn from previous experience of negative Phase III trials that were based on positive Phase II data?

Background:

Currently riluzole remains the only pharmacological intervention with widespread approval as a disease-modifying agent for ALS. Despite positive effects in animal models or phase II trials, numerous promising therapeutics have failed during phase III efficacy studies over the last 20 years. Thus, a re-appraisal of phase III methodologies is warranted.

Rationale 8-1-1 (target engagement):

Target engagement: Many of these trials lack evidence of the therapeutic either reaching the CNS or engaging the intended target (EVID).

Recommendation 8-1-1:

a. Investigators should include measures of target engagement by the therapeutic molecule.
b. Investigators may include evidence of CNS penetration if warranted.

Rationale 8-1-2 (phase III trials):

Add-on designs within double-blind placebo controlled trial (e.g. xaliproden, pentoxyfilline, minocycline) may have reduced the potential efficacy of the investigated drug due to interactions with riluzole: (PRIN).

Recommendation 8-1-2:

a. Investigators should prespecify sub-analyses to examine riluzole.
b. Because riluzole might mask potential efficacy of the tested drug, investigators may consider a placebo controlled group free of riluzole if allowed by local ethics board.

Rationale 8-1-3 (outcome measures):

More efficient outcome measures are needed, including those that combine function (Phases II and III) and survival (phase III) (EVID).
Recommendation 8-1-3:

Investigators should develop more efficient outcome measures, including combination measures, that reflect the target of the treatment.

Rationale 8-1-4 (heterogeneity of ALS):

Phenotypic and genotypic heterogeneity of the ALS population have not typically been considered in the classical criteria of inclusion in previous trials (EVID). Due to difficulties in defining appropriate homogeneous subgroups of ALS patients, trials may have failed to enrich study populations tailored to a specific treatment (EVID). Consequently, clinicians should determine the best ALS-group for a given therapeutic (INFER).

Recommendation 8-1-4:

a. Investigators should recognize ALS genotypic and phenotypic heterogeneity, and, where applicable, enroll only patients anticipated to benefit based upon presumed mechanism of action of therapeutic intervention. (see 2A1, 2B1)
b. Investigators should stratify as appropriate to the trial design. (see 2A2,2C1,3)
c. Negative phase III trials should be followed by hypothesis-generating sub-group analysis to better understand the heterogeneity of the disease.

8-2. Patient-led trials and self-experimentation by PALS

Background:

People living with ALS (PALS) are pursuing novel treatments outside of mainstream clinical trials. For example, patients independently took lithium and reported their experiences in a patient forum. The term “patient-led trials” has been used to describe such self-experimentation by PALS. On a smaller scale, PALS often report anecdotal experiences managing symptoms that may have broader applicability.

Rationale 8-2-1:

Self-experimentation does not adhere to established clinical trial methodology, and therefore cannot obtain valid, generalizable results (EVID). In some cases, self-experimentation or anecdotal observations, particularly those describing symptom relief, may generate hypotheses that could inspire further investigation (INFER).

Recommendation 8-2-1:

Investigators may include anecdotal observations made by PALS in the process of hypothesis generation for future clinical studies, particularly if biologically plausible.

Rationale 8-2-2:

For PALS, the investigation and approval processes, even if successful, can easily be longer than their disease course (EVID). Approval of novel treatments requires a sufficient evidence base (EVID). In this context, self-experimentation reflects an interest among PALS to accelerate access to potentially beneficial interventions (INFER). The risks taken during patient self-experimentation reflect the urgent need to identify, and provide prompt access to, more effective therapies for ALS.
**Recommendation 8-2-2:**

Investigators should minimize time between completion of trials and reporting of complete results. Investigators should advocate for open label extension in appropriate circumstances.

**8-3 Regulatory, Off Label and Pragmatic Trials**

**Background:**

Clinical trials fall into three broad categories: regulatory trials, investigator-initiated trials and pragmatic (post approval) trials. Regulatory trials aim to evaluate the efficacy of a new intervention in a well-controlled setting with the aim of obtaining regulatory approval. Similarly, investigator-initiated trials using approved drugs, if positive, may follow the development path to approval for a new indication.

The NIH definition of a pragmatic trial is one in which approved drugs are tested in real world settings. Pragmatic trials have weak internal validity but strong external validity, overlap with phase IV trial designs and are more likely to be investigator-initiated trials rather than industry-sponsored trials. Pragmatic trials may become a future consideration as new therapies are proven to affect the course of the disease. Furthermore, there are several currently utilized treatments for sialorrhea, spasticity, depression, and other symptoms related to ALS that may warrant such investigation.

Comparative effectiveness research represents a particular form of pragmatic trial designed to evaluate the comparative effectiveness of more than one effective intervention. In comparative effectiveness research, innovative study designs and analysis aim to determine the comparative effectiveness, post approval, in a clinic setting. Interest in comparative effectiveness research has grown, since the establishment of the Patient Centered Outcomes Research Institute (PCORI), a federally funded entity to focus on areas of need, with strong patient engagement. For novel therapies, the regulatory path is designed to protect patients and to identify therapies that meet the highest level of proof of efficacy in a well-defined patient population.

**Rationale 8-3-1:**

Investigator-initiated trials in ALS often involve therapies that have been studied and approved for other indications (EVID). These trials take advantage of safety profiles in other disease states. Ongoing development followed a regulatory path to drug development; while the studies were ultimately negative, the approach shows promise in identifying potentially useful therapeutic agents (PRIN).

**Recommendation 8-3-1:**

Investigators should initiate clinical trials in ALS only when preclinical studies are sufficiently compelling and when a measure of target engagement is available to determine a biological effect.

**Rationale 8-3-2:**

Although regulatory trials have produced only one approved therapy to alter disease course in ALS to date, the process has been successful in other diseases (EVID). A lack of positive trials does not necessarily indicate a flawed process. Rather, the negative trials may reflect other
factors, such as lack of substantial efficacy, limited biomarkers, and limited sensitivity of the outcome measures (INFER).

**Recommendation 8-3-2:**

Investigators must continue to aggressively pursue disease-modifying therapies, utilizing the scientific method that is inherent in regulatory compliant trials to increase the likelihood that therapies become available to people with ALS.

**Rationale 8-3-3:**

Regulatory trials are dependent upon strong preclinical data, appropriately sensitive primary and secondary outcome measures, and biomarkers that can guide go/no go decision-making in phase I and II trials (PRIN). The interferons in multiple sclerosis were initially approved on the basis of changes in imaging (EVID). The use of pulmonary function and strength measures, may add sensitivity to identify change while still meeting the criteria of patient and disease relevance in conjunction with preclinical data on viable mechanisms of action (EVID).

**Recommendation 8-3-3:**

Investigators must identify more sensitive indicators of survival and function in addition to the ALSFRS-R (INFER). When relevant, investigators should utilize validated biomarkers to identify patient subsets most likely to benefit from the type of intervention being tested, based upon the presumed mechanism of action.

**Rationale 8-3-4:**

The cost of drug development programs is a deterrent to ALS drug development (EVID). The orphan disease program of the FDA and EMEA enables a more streamlined process for positive trials, with pre-registration meetings, significant tax credits, and the option to seek approval with one, rather than two, positive phase 3 trials (EVID). Investigators should not include efficacy as a primary endpoint in trials that are designed and powered for safety, tolerability and dose finding (PRIN).

**Recommendation 8-3-4:**

Investigators must take full advantage of FDA and EMEA programs for ALS drug development. Principal investigators may include pre-specified analysis of subgroups as well as futility analysis to prevent expensive negative trials.

**Rationale 8-3-5:**

Clinical trials are performed to establish a new intervention in a well-defined population of research participants (PRIN) Successful interventions, both symptomatic and disease modifying, may benefit from subsequent evaluation in the pragmatic trial setting for safety and efficacy in the ‘real-world’ ALS population (INFER).

**Recommendation 8-3-5:**

Investigators should perform well-designed pragmatic (Phase IV) trials on therapeutic interventions for ALS symptoms and, when available, for ALS disease-modifying agents.
Rationale 8-3-6:

Many PALS are excluded from current regulatory phase II and phase III trials. Comparative effectiveness research generally involves broader inclusion criteria, providing an opportunity for more PALS to participate in clinical research and ultimately to help improve ALS care (EVID). The notable limitation of comparative effectiveness research in ALS currently, however, is that only one effective treatment exists (PRIN). Thus, the opportunities for evaluating interventions to slow ALS disease progression are limited (INFER). Nonetheless comparative effectiveness research is an attractive mechanism for evaluation of symptomatic therapies (PRIN). Furthermore, some symptomatic therapies might reduce the incidence of life-threatening complications of ALS (PRIN).

Recommendation 8-3-6:

Investigators should utilize comparative effectiveness research and other pragmatic trial designs to compare established interventions and to determine the external validity of positive phase III trials.

References: