INTHENews

# The Making of Revised Guidelines for ALS Clinical Trials

In the field of motor neuron disease, more specifically amyotrophic lateral sclerosis (ALS), we previously had only one disease-modifying drug, Riluzole, which was approved by the U.S. Food and Drug Administration (FDA) almost 24 years ago. In the summer of 2017, the FDA approved a new intravenous medication, Edaravone. We now have two approved medications, but their benefits are modest at best. We are still in desperate need of more effective medications.

*Airlie House ALS Clinical Trials Guidelines Workshop*

In the past 2 decades, more than 50 medications were tested in randomized clinical trials, but unfortunately, most of these medications did not demonstrate benefits. Every ALS stakeholder (patients, families, doctors, researchers, disease advocacy groups, funding agencies, regulatory officers and more) asks why developing effective medications is so challenging. One answer is that we simply have not discovered really effective medications. Have our basic science colleagues introduced the right medications to us? Do the medications developed have target engagement? Have we developed the right design to conduct these clinical trials? These are all legitimate and important questions.

What we clinicians and clinical trialists can do for the entire field is to improve clinical trials themselves. When clinical trials in ALS became quite active in the 1990s, consensus guidelines were developed and published by Dr. Robert Miller and his colleagues in 1999. We have had many clinical trials since that time, and we thought it was time to renew and update the 18-year-old guidelines.

In 2015, a group of volunteers gathered and established steering and advisory committees. After discussions and meetings with many experts, we held a large international workshop to accomplish our goal. Held from March 13–16, 2016, we had more than 140 international attendees present, including PALS (patients with ALS), ALS Advocacy groups, clinicians and clinical trialists, basic scientists, biostatisticians, regulatory agency officers from the USA and Japan, and EMI from all over the globe. We had tremendous intellectual experts present, including Drs. Ben Brooks and Bob Miller. The picture shows all attendees who worked very hard to develop the new ALS guidelines.

With great fortune, we received many grants and donations to support the workshop and new guidelines development. Our sponsors included MDA, the National Institutes of Health, ALS Association, British Motor Neurone Disease Association, ALS Canada, Adams Foundation, Japanese ALS Association, International Alliance of ALS/MND Associations, and pharmaceutical companies, including Biogen, Cytokinetics, Mitsubishi-Tanabe, Knopp Neuroscience, Avanir, and Sumitomo Dainippon Pharma. >

In the beginning, we simply thought we could develop evidence-based guidelines; however, there was not enough evidence in the field of clinical trial design and implementation. We realized that we needed an expert and asked Dr. Gary Gronseth for his guidance. Dr. Gronseth is a stroke specialist, chair and professor of Neurology at University of Kansas, and he served as the Principal Methodologist for the American Academy of Neurology guidelines development. I must tell you that he spent countless hours towards the consensus process, and without his guidance, we would not have been able to develop evidence-informed consensus guidelines.

We addressed nine areas of need within ALS research:

1. Pre-clinical studies
2. Biological and phenotypic heterogeneity
3. Outcome measures
4. Disease-modifying and symptomatic interventions
5. Recruitment and retention
6. Biomarkers
7. Clinical trial phases
8. Beyond traditional trial designs
9. Statistical considerations

Before the workshop, all attendees were assigned to one of eight sections. Two section leaders for each section generated a draft set of guidelines, including a "background" for developing (pre)clinical questions and a "rationale" outlining the evidence and expert opinions. Following this method, we developed the first draft guidelines before the Workshop. The drafts focused on the logical rationale for the guidelines, validity of the axiomatic and evidence statements, logical basis of any inferences, and the absence of any necessary premises.

After the workshop, the guidelines were further edited and improved, incorporating discussion points from the workshop. The first guideline draft was disseminated widely through the internet, and we asked the public to provide comments during the summer of 2016. We received many comments, which were each promptly addressed. Each section met again independently to review the feedback and provide modifications to their draft's background, rationale, and guidelines. This resulted in a second draft from each of the eight sections.

In the winter of 2017, we started the modified Delphi consensus process. Each member of each section made comments on the document and anonymously voted for each background, rationale and guidelines (a total of 112). This process was repeated three times until the voting reached unanimous agreement (more than 80% agreement). The degree of agreement at the end provided strength for each recommendation (delegated as must, should or may consider).

In the fall of the 2018, the Delphi consensus process was completed and the final guidelines were developed. The Writing Committee, led by Dr. Leonard van den Berg, Netherlands (including Eric Sorensen, Gary Gronseth, Ben Brooks, Robert Miller and myself), started to work on the manuscript. There were too many guidelines (112 in total); therefore, the section leaders voted on the most important and practical guidelines to be included in the manuscript. Fifteen guidelines were selected for the main manuscript. In reality, we managed to include more. Further, we had three appendices, including a large glossary to define difficult terms and all 112 guidelines, along with backgrounds and rationales. (For anyone who reviews the paper and wishes to look at the appendices, they should click "Dryad" immediately below the Results heading of the PDF.) We also included a section for statistical considerations (excluded from the Delphi process), which was written by statistical experts. The final manuscript was submitted for publication in Neurology in the spring of 2018 and accepted in December of 2019.

This process sounds tedious and time-consuming; however, we are all confident that this is the best consensus document for future ALS clinical trials. We hope investigators who plan to conduct clinical trials in ALS refer to this document for guidance and consultation. We state in the end of the Discussion section, "Given the rate at which the field has advanced in recent years, we suggest a follow-up meeting to refine the guidelines within four years. Moreover, we view the 2018 clinical trial guidelines not as inflexible, final or complete, but rather as an updated starting point for improving clinical trial design and accelerating the development of effective treatments for patients with ALS."

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