September 16, 2020

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA-2020-D-1136-0020: Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency - Guidance for Industry

Dear Sir or Madam,

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or "Agency") for the opportunity to comment on the Agency's Guidance entitled, "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency - Guidance for Industry". We are grateful for the Agency's efforts to ensure therapeutic development and regulatory review of new therapies for neuromuscular diseases is not decelerated due to the pandemic.

On April 29th, we filed comments to FDA in response to the Agency's "Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency." We thanked the FDA for the flexible approach exhibited towards clinical trial amendments exhibited in the Guidance while requesting additional information and clarity on certain key points. These included, but were not limited to:

- Adapting neuromuscular clinician reported (ClinRO) assessments and performance outcome (PerfO) assessments from clinical settings to home settings without losing statistical integrity.
- Integrating new home-based clinical outcome assessments into ongoing or enrolling clinical trials.
- Approaches to missing data, interpretation of patient retainment issues within ongoing clinical trials, and options for ending data collection earlier than previously planned.
- Changing study administrators or administration location due to COVID-induced closures or changes in medical professional availability.

We are grateful that many of these questions have been answered in subsequent updates to the Agency's "Conduct" guidance, and we are similarly grateful that these issues are further explored within this guidance on statistical considerations. We address FDA's approach on these issues as they pertain to the neuromuscular disease patient's experience in ongoing clinical trials below.

Approaches to "Missing Data" Due to COVID-19 Impacts:

We are grateful for FDA's advice on how to approach missing data within a clinical trial due to COVID-19. In our April comments, we asked FDA to clarify how the Agency would advise clinical trial sponsors to adjust for missing data due to the loss of trial sites or scheduled data collection visits, or enrollees dropping out of the trial.

First, in this guidance, FDA suggests that "A sponsor can consider increasing enrollment after the impact of COVID-19 has passed, as appropriate, over the originally planned enrollment to overcome the loss of information from the impact of COVID-19." In rare diseases, including some very rare NMDs, this may not be possible as much of the eligible population for the trial may already be enrolled. Furthermore, those additional patients who may be eligible and enrollable may be difficult to reach or far away from trial sites and may be particularly averse to travel during a pandemic.

Consequently, we ask FDA to consider issuing further guidance and advice on alternatives to re-opening enrollment in rare disease clinical trials if additional participants cannot be enrolled. Such guidance could include advice on amending inclusion/exclusion criteria to allow for a larger cohort of patients to be able to enroll. We understand such expansions could jeopardize the integrity of trial, so we encourage FDA to issue further guidance on this issue.

Second, FDA similarly suggests that trial sponsors consider "removing all participants from closed sites who were scheduled for an endpoint ascertainment from the analysis" as a means to approaching missing data due to closed trial sites. Again, while this may work in clinical trials with a large number of enrolled participants, in rare diseases, this may compromise the integrity of the trial as losing only a handful of enrollees could compromise the statistical power of the trial. We appreciate the additional options discussed in item (6), but if these options are the primary approaches to sustaining rare disease clinical trials in ways to keep as many patient participants in the trial as possible, they deserve further discussion.

Finally, we would like to emphasize the importance of clinical trial participation to many in the neuromuscular disease patient population, and removal from the clinical trial due to missed visits caused by COVID-19 would be a devastating setback to many patients and their families. We encourage FDA to emphasize approaches that keep all enrollees enrolled in the trial even if they have missed administration or data collection visits.

Approaches to Modified Endpoints

FDA also issues suggestions for modifying primary and secondary endpoints if data collection in the previously established endpoint proves infeasible. This may occur due to site closures or site rules that prevent the trial participant from traveling to the site to complete the assessment, or the assessment, such as certain pulmonary function tests, are unsafe to conduct during the pandemic.

In our April comments to FDA, we asked FDA for further guidance on when and how to modify endpoints due to the pandemic, and we are pleased this is further addressed as part of this guidance. FDA endorses the possibility of:

a. “Using alternative ascertainment methods, such as replacing in-person endpoint ascertainment based on performance outcomes or interview-based clinician-reported outcomes with remote ascertainment…
c. For a composite endpoint, including additional and clinically relevant components or removing components that cannot be ascertained
d. For a binary endpoint that is based on a continuous or ordinal measurement, using the continuous or ordinal measurement as the endpoint.”

While it is valuable for FDA to endorse each of these options, it would be even more valuable for the Agency to expand this discussion by further detailing when certain approaches are necessary or appropriate, particularly within rare neuromuscular disease clinical trials.

For example, it would be valuable to understand under what circumstance a PerfO measure can be transitioned from the clinic to the home, or when a certain ClinRO measure can be conducted over video, and when it cannot. These details are important to sponsors as they are approaching alterations to the measurement of their primary and secondary endpoints.

Approaches to Closing a Clinical Trial Early due to COVID-19:

In our April comments, we asked, “How does the Agency advise sponsors to approach potentially closing a trial earlier than previously planned if continued data collection is arduous or impossible?” We are pleased that this issue is addressed in this guidance as FDA posits that interim analyses or the initially-planned statistical analysis, only earlier than anticipated, may still be adequate if statistical power is not overly compromised and statistical inference is still possible.

This may be more challenging, however, for rare disease clinical trials as the loss of data due to early trial closure may be more compromising to statistical power and inference due to fewer data being present in the first place. For clinical trials that are already small, and thus already face statistical challenges, we encourage FDA to consider how this guidance could be applied in small rare disease clinical trials.

In conclusion, we are grateful for FDA’s continued commitment to working with sponsors and the stakeholder community to adapt to the challenges brought upon by the pandemic. For questions regarding MDA or the above comments, please contact me at 202-253-2980 or at pmelmeyer@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs