



April 29, 2020

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

**Re: Docket No. FDA-2020-D-1106: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic**

Dear Sir or Madam,

On behalf 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, “FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic”. We are grateful for the Agency’s efforts to ensure continued successful therapeutic development of NMD therapies during the COVID-19 Public Health Emergency (PHE), and we respectfully submit additional topics of consideration for further FDA guidance and advice.

We appreciate the Agency’s rapid publication of the March 18th Guidance and subsequent “Frequently Asked Questions” (FAQ) published on April 2<sup>nd</sup> and April 16<sup>th</sup>. This pandemic requires rapid responses to ongoing challenges, including in therapeutic development, and swift and proactive action from FDA is essential. Additionally, we are thankful for FDA’s flexible approach in considering and facilitating protocol amendments and necessary additional changes to clinical studies to keep trial participants safe and adherent to social distancing and “stay at home” guidelines.

Perhaps in no other disease area is such a flexible response more needed. Neuromuscular diseases can be multisystemic, often affecting the organ systems (such as pulmonary and cardiac) most compromised by COVID-19 infections. These conditions can also be irreversibly degenerative, sometimes rapidly, underscoring the immediate need for therapeutic intervention. This tension between the dangers of participating in clinical trials during a pandemic and the dangers of the neuromuscular diseases themselves require careful and methodical approaches to the risks and benefits of continuing clinical trials for the NMD patient population.

Consequently, we agree with FDA’s proposal of a deliberately flexible approach to clinical trials during this pandemic in addition to asking for further guidance from FDA in certain areas.

**Greater Guidance on Clinical Trial Changes:**

We appreciate that FDA put forward a clear process for submitting protocol amendments to the Agency, as well as advice on how to approach the evolving risks and benefits of continuing to conduct clinical studies during the PHE. In the FAQs published on April 16<sup>th</sup>, FDA further

clarifies the appropriate processes and procedures for considering how to move investigational product (IP) administration as well as performance outcome (PerfO) and clinician reported outcome (ClinRO) assessments to local sites or the home.

However, further clarification from FDA on how to approach certain challenges specific to neuromuscular diseases and similar conditions would be helpful. First, in neuromuscular diseases, many, if not most, validated endpoints widely used in clinical studies (such as the 6-minute walk test, upper limb motor scales, respiratory function tests, and several others PerfOs) rely on capturing an enrollee's performance in these assessments in controlled clinical settings. We are concerned that if trial sponsors choose to collect such data in clinical settings closer to the home, or even within the home, of the trial enrollee to avoid travel, FDA could call into question the integrity of the data collected.

We ask FDA to issue further guidance on how to transition data collection that utilizes commonly used endpoints in neuromuscular diseases from the clinic to the home or other location in a manner that preserves the integrity of the trial. In the April 16<sup>th</sup> update, FDA cites the 6-minute walk test as a PerfO that may not be safe to transition to a home setting. How does FDA advise sponsors to set up 6-minute walk test or other timed function test courses in the home that are safe, and that will maintain the integrity of the data collected? Similar questions arise with other PerfOs. For example, what method and procedures should sponsors implement to facilitate forced vital capacity testing at home? What guidance can FDA offer to transition upper limb motor scale data collection from the clinic to the home?

Additionally, we ask FDA to issue guidance on what alternative clinical outcome assessments and endpoints can be chosen that are specifically intended for home use. These could include clinical outcome assessments that track movement through wearables or video assessments. FDA has already accepted letters of intent for two innovative clinical outcome assessments in Duchenne muscular dystrophy (DMD) that could be considered, as well as other innovative functional movement assessments in development that could be accelerated to allow for clinical trials to commence or continue in the home.

Second, we ask the Agency to issue further guidance on the continuation of data collection efforts at different stages of clinical studies, and how sponsors should approach the risks and benefits of collecting these data given their relative impact. For example, should sponsors approach the risks and benefits of baseline data collection any differently than collection of secondary or tertiary outcome data? Such guidance will assist sponsors, sites, and IRBs as they consider the relative risks and benefits of the continuation of certain aspects of clinical studies.

Third, with expected clinical trial attrition to increase substantially due to patients deciding the risks of continuing trial participation outweigh the potential benefits, how will FDA view attrition due to COVID-19 when other attrition reasons (adverse events, side effects, lack of benefit) may also be present? Further clarification from FDA on how the Agency will view high attrition rates would be appreciated.

Finally, further guidance from FDA on how the Agency will assess the following PHE-caused events would offer greater clarity to trial participants and sponsors:

1. Loss of investigators or trial sites: If a trial requires a change in investigators or trial sites due to the PHE, how does FDA advise sponsors to approach such changes? We thank FDA for the April 16<sup>th</sup> FAQs pertaining to change in investigators, and with this information, we are confident sponsors should be more confident in utilizing local medical professionals in the conduct of the trial. However, will FDA have any concerns related to the integrity of the trial if investigators or study monitors are changed midway through the trial?
2. Early conclusion to trial: In some cases, trials may end early if they are near their previously expected closure dates, and trial continuation is proving to be difficult, perhaps impossible, due to the PHE. How does the Agency advise sponsors to approach potentially closing a trial earlier than previously planned if continued data collection is arduous or impossible?
3. Off-schedule data collection: In many cases, sponsors may not be able to collect necessary data from trial enrollees on the pre-determined date as enrollees may not be able to attend the needed monitoring appointment. In such cases, how will FDA view data collected on an off-schedule date if on-schedule monitoring visit proves impossible?
4. Change in administration location: For many trial participants, administration of the experimental therapy may need to take place in an alternate location from previous administrations, such as at a clinic closer to home, or in the home itself. We are thankful for FDA's additional guidance in Q.15 of the April 16<sup>th</sup> FAQs, but further information on how the Agency will assess the impacts of the change of administration location on trial integrity would be beneficial.
5. Change in medical professionals administering trial requirements: Similarly, while Q.15 addresses if and how to employ local investigators and monitors if travel to trial sites is infeasible, further guidance on preserving data integrity with new trial investigators or monitors would be helpful.
6. Changes in Endpoints: We are aware that certain clinical outcome assessments, such as pulmonary function testing, may no longer be permitted by medical centers due to the increased risk of contracting COVID-19 associated with such tests. How will the Agency approach changes in endpoints within trials if the testing of previous endpoints are no longer safe or allowable under the PHE?

With further information and guidance from FDA in hand, we believe sponsors of neuromuscular disease clinical trials will be better equipped to continue their trials during this PHE. This is incredibly important to the NMD community, many of whom are counting on ongoing clinical trials to deliver the very first safe and effective therapy for their condition.

### **Consistent Guidance and Approach Across and Within Medical Centers and Review Divisions:**

Within the Guidance and accompanying FAQs, the Agency affords review divisions enormous flexibility in guiding sponsors on how to continue clinical trials. Extensive flexibility is certainly warranted, as each experimental therapy, clinical trial, patient population, trial site structure, and more are unique and can be impacted quite differently by the PHE. However, we ask FDA for greater assurances that flexible approaches towards the continuation of clinical trials are

consistently applied both within review divisions, as well as across review divisions and medical centers. We are concerned that the great amount of deference publicly given to review divisions to assess how to proceed with clinical trials could result in disparate approaches. Consequently, we ask the Agency to provide a more deliberate, flexible approach towards clinical trials within further iterations of the Guidance and FAQ.

**Effects on FDA’s Ongoing Review Capacity:**

Finally, given FDA’s clear and appropriate “all hands on deck” approach to tackling the PHE (for which we are thankful for the Agency’s dedication), there are some concerns within the neuromuscular disease community that this will hinder the Agency’s ability to swiftly but thoroughly review new therapies for the neuromuscular disease community.

Given that FDA has publicly announced a reallocation of resources internally within the Agency to address the PHE (such as in the Coronavirus Treatment Acceleration Program [CTAP]), we ask for more information on how this may impact neuromuscular disease product reviews. Is FDA anticipating any impact on meeting PDUFA dates and other impactful deadlines? Should the neuromuscular disease community expect any slow in review times or Agency ability to guide sponsors on non-COVID-19 related efforts? Further clarity would be welcomed.

In conclusion, we are grateful for FDA’s rapid and thorough response to the COVID-19 pandemic, as well as the Agency’s swift and resolute actions to accelerate access to medical devices in shortage, treatments for the disease, and potential vaccines. We are similarly grateful for the necessary flexibility granted to trial sponsors as they navigate the complexity of clinical trial continuation. We ask that as FDA considers further guidance to sponsors, the Agency considers our recommendations for further clarity. For questions regarding MDA or the above comments, please contact Paul Melmeyer, Director of Regulatory Affairs, at [pmelmeyer@mdausa.org](mailto:pmelmeyer@mdausa.org).

Sincerely,



Paul Melmeyer, MPP  
Director of Regulatory Affairs