August 6, 2019

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

Re: Docket No. FDA-2019-D-1264: Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry

Dear Sir or Madam,

The Muscular Dystrophy Association (MDA) thanks the Food and Drug Administration (FDA or "Agency") for the opportunity to comment on the Agency's draft guidance entitled "Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry".

MDA is the nation's leading nonprofit organization dedicated to transforming the lives of individuals living with muscular dystrophy, ALS, spinal muscular atrophy and other neuromuscular diseases through innovations in science and innovations in care. MDA fulfills its mission by funding biomedical research, providing access to expert clinical care and support through its national MDA Care Center Network which is comprised of expert medical clinics at more than 150 of the top health care institutions across the US, and by championing public policies and programs that benefit those we serve. Since inception, MDA has invested more than $1 billion in research grants to accelerate treatments and cures for neuromuscular disorders, making MDA the largest source of neuromuscular disease funding in the U.S. outside of the federal government.

While progress in therapeutic development efforts has been moving forward at a rapid pace in many neuromuscular disorders, the majority of individuals living with neuromuscular diseases still have no therapies to treat the underlying cause of disease, and there are no cures. As of today, of the over 40 neuromuscular diseases represented by MDA, only a few (spinal muscular atrophy, Duchenne muscular dystrophy [DMD], amyotrophic lateral sclerosis [ALS], myasthenia gravis, Lambert-Eaton myasthenic syndrome, carnitine deficiency, and Pompe) have an FDA-approved treatment. And for those disorders where a therapy is currently available to patients, the treatments can be limited to a subset of patients who demonstrate a specific genetic mutation, for example, that would be amenable to the intervention.

Thus, clinical trials, including the ability to participate within clinical trials, are essential to the continued progress in combating neuromuscular disease.

For these reasons, MDA is pleased to comment on FDA's draft guidance as eligibility, enrollment, and design of clinical trials are critically important to patients with NMDs. Not only are neuromuscular disease patients counting on clinical trials to potentially deliver safe and effective treatments for their disease, but many NMD patients also rely on participation in clinical trials as the only option to treat their condition. While MDA applauds several progressive and innovative proposals for structuring clinical trials contained within the draft guidance, we believe the draft guidance could still be further strengthened to facilitate the participation of patients with NMDs in clinical trials.

Limitations in Access to Clinical Trials for Individuals with Neuromuscular Diseases:

There are numerous barriers to participating in clinical trials for individuals living with neuromuscular disease. These barriers come in many forms—from trial design, to the ability to travel to a trial site, to understanding what clinical trials are even available that they may qualify to participate in.

Knowing that such barriers exist and in the interest of having a greater understanding of the magnitude of the challenges, in 2018, MDA surveyed the NMD community to better understand and capture the daily experiences of those living with NMDs, including gathering insights around clinical trials. Over 3,300 patients and caregivers responded, and MDA published the results entitled "ONEVoice: Insights and Observations from a National Survey of Adults and Families Living with Neuromuscular Disease" ("ONEVoice") in December 2018. Included within this survey were questions pertaining to issues the NMD community face in accessing and participating in clinical trials.

- With regard to knowledge of clinical trials, "ONEVoice" found that only 53 percent of patients with an NMD felt that they were "very" or "somewhat" knowledgeable of clinical trial options, with only 9 percent responding "very knowledgeable."[1] Caregivers were slightly more knowledgeable with 13 percent responding they were "very knowledgeable" and 50 percent responding they were "somewhat knowledgeable."[2]
- With regard to the interest in participating in clinical trials, the survey revealed that 79 percent of patients surveyed indicated that they were "very interested" or "interested" in learning more about clinical trials, with an identical 79 percent of caregivers concurring.[3]
- Perhaps most notably, the vast majority of patients surveyed—66 percent—indicated that they would be interested in participating in a clinical trial, but never have.[4]

[1] ONEVoice: Insights and Observations from a National Survey of Adults and Families Living with Neuromuscular Disease (2018, December 9). Retrieved August 1, 2019, from https://www.mda.org/sites/default/files/2018/12/MDA_OneVoice_Whitepaper.pdf
[2] *Ibid.*
[3] *Ibid.*
[4] *Ibid.*

- When asked about the main impediments to participating in a clinical trial, 44 percent responded that they have not been asked to participate. 39 percent indicated that they did not know about clinical trial options, and 29 percent reported that trial sites were too far to travel to, 21 percent believed that trial was not available for their disease, and 19 percent said that they did not qualify for ongoing trials.[5]

Education and Awareness:

The results of MDA's "ONEVoice" survey underscore the importance of outreach and education to the NMD community to ensure they are aware of clinical trial options. This is why MDA has launched efforts to educate the NMD community on their clinical trial options, including integrating the Clinical Trial Finders Tool onto MDA's website to assist patients in finding the right clinical trial for them.[6] MDA also publishes ongoing clinical trial opportunities in our " MDA Monthly Report.[7]

While education and awareness issues for enrolling clinical trials are briefly mentioned by FDA (lines 250 through 252) within the guidance, we recommend the Agency expand its discussion on best practices for industry to consider when conducting outreach to patients to ensure broad awareness of clinical trial opportunities.[8]

FDA could consider requiring comprehensive outreach and enrollment plans to be discussed with the Agency at the outset of a trial to ensure sponsors will achieve broad awareness of their trial. FDA should also request that the sponsors communicate with patient organizations in the disease space. While FDA recommends coordination with patient organizations on lines 304 through 308, greater emphasis on collaborative enrollment and awareness practices, as well as further FDA instruction, could be warranted.[9]

Travel Limitations:

Many individuals with NMDs face particularly daunting travel challenges due to ambulatory limitations. Patient respondents to MDA's "ONEVoice" survey rated "Independence regarding mobility/getting around" as their top concern (64 percent of patients).[10] These access limitations also prevent individuals with NMDs from participating in clinical trials as 29 percent of patients surveyed listed "distance to travel site" as a reason for why they did not enroll in a trial.[11]

To address these limitations, MDA has advanced a variety of initiatives aimed at reducing travel barriers. MDA provides an accessible air travel resource center that houses airline accessible

---

[5] *Ibid.*
[6] MDA's Clinical Trials Finder Tool can be accessed here: https://www.mda.org/research/clinical-trials
[7] MDA's Monthly Reports can be accessed here: https://www.mda.org/science/mda-monthly-report-for-healthcare-providers-and-researchers
[8] Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry, 84 FR 26687 (June 7, 2019), pg. 8
[9] *Id.*, at 9
[10] ONEVoice: Insights and Observations from a National Survey of Adults and Families Living with Neuromuscular Disease
[11] *Ibid.*

travel policies and options in a central location for the NMD community.[12] MDA has worked closely with the Department of Transportation and Federal Aviation Agency in implementing the Air Carrier Access Act, among other policy interventions, to make air travel more accessible for the NMD community. MDA also supports the Air Carrier Access Amendments Act (S.669 and H.R.1459) which would further strengthen and update airline accessibility standards and policies for individuals with disabilities.

In its draft guidance, FDA acknowledges these travel limitations, stating, "A trial requiring participants to make frequent visits to specific sites may result in added burden for participants, especially the…disabled and cognitively impaired individuals who require transportation or caregiver assistances."[13] FDA continues, stating, "For individuals under current clinical care on a regularly scheduled basis, additional clinical trial study visits may be burdensome and a disincentive for enrollment in clinical trials."[14]

In response, the Agency recommends that sponsors, "consider the recruitment challenges that may occur because of the planned visit schedule: reduce the frequency of study visits to those needed to appropriately monitor safety and efficacy…or mobile technology tools can be used to replace site visits and provide investigators with real-time data."[15] FDA continues by recommending that sponsors, "offer and make participants aware of financial reimbursements for expenses associated with costs incurred by participation in clinical trials."[16]

MDA is strongly supportive of each of these acknowledgements and subsequent recommendations and asks FDA to further expand on how sponsors can make their trials as accessible as possible to individuals with travel limitations. We are particularly supportive of the suggestion to develop mobile technology tools that can replace site visits. These tools can allow patients to stay in their home while still tracking the progression of the disease or impact of the treatment. Telemedicine technologies can facilitate screening for inclusion/exclusion criteria in the home, obviating the need for enrollment clinic visits for those wishing to participate. Mobile technologies also hold the promise of collecting data for innovative clinical outcomes assessments that better measure the progression of disease or therapeutic efficacy while also allowing patients to stay home.

Eligibility and Inclusion/Exclusion Criteria:

Many individuals with NMDs who are aware of clinical trials, and willing to travel, are still unable to participate due to the trial's design, including the inclusion/exclusion criteria. Often patients with the most severe forms or most significant manifestation of disease, including those who require ventilation or a feeding tube, are excluded. Others may be excluded because they lost ambulation and the primary endpoint for the trial relies on being ambulatory. Others are

[12] MDA's Accessible Air Travel Resource Center can be found here: http://cqrcengage.com/mda/accessibleairtravel?0
[13] Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs; Draft Guidance for Industry
[14] *Ibid.*
[15] *Id.*, at 7
[16] *Ibid.*

deemed too young or old, perhaps even not advanced in disease progression enough to participate.

This can be particularly problematic to those in the NMD community as there may only be one trial available at any given time, and if excluded, patients have no other options for treating their disease. Furthermore, most NMDs are progressive and irreversibly degenerative, and patients do not have the luxury to simply wait for the next trial to commence.

Consequently, clinical trial eligibility criterion for NMD therapies must reflect the dire and urgent situation in which many NMD communities find themselves. However, FDA does little to convey an understanding of this urgency, and of clinical trials as anything more than research endeavors to understand the safety and efficacy of a potential treatment. FDA must understand that clinical trials are often the only hope for NMD patients facing terminal diseases. MDA implores the Agency to reflect this urgency in the draft guidance.

While FDA does not emphasize the importance of broad trial eligibility for seeking immediate therapeutic intervention, the Agency does convey an understanding of the importance of broad eligibility criteria in other ways. For example, FDA states,

> "…failure to include complex participants in a development program may lead to a failure to discover important safety information about use of the investigation drug in patients who will take the drug after approval. Therefore, broadening eligibility criteria, when appropriate, maximizes the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice, without jeopardizing patient safety."[17]

Furthermore, FDA encourages sponsors to use eligibility criteria "that will allow the clinical trial population to reflect the diversity of the patients who will be using the drug if the drug is approved."[18] FDA encourages sponsors to consider eliminating each criterion that is not "needed to help assure the safety of trial participants or to achieve the study objectives when developing clinical trial protocols."[19]

FDA even goes so far as to encourage the use of adaptive trial designs and open-label studies. Adaptive trial designs would allow for patients of varying disease presentations to participate at different stages of the trial. FDA also encourages the use of "an open-label extension study after early-phase studies to encourage participation by ensuring that all study participants, including those who received placebo, will ultimately have access to the investigational treatment."[20]

Each of these suggestions are substantial steps in the right direction, and MDA thanks FDA for encouraging such a flexible, inclusive direction for clinical trial eligibility criteria. The promotion and encouragement for the broadest possible eligibility criteria, adaptive trial designs, and open label studies are all steps in the right direction for the NMD community and we urge

[17] *Id.*, at 3
[18] *Id.*, at 4
[19] *Ibid.*
[20] *Id.*, at 10

the Agency to continue focusing on these critical matters that are essential for greater clinical trial participation.

While we are pleased with each of these aspects of the draft guidance, MDA suggests that the Agency readdress the language on enriched clinical trials. By their very nature, enriched clinical trials exclude various cohorts of individuals living with NMDs, particularly those with the most complex manifestations, or those who are not treatment naïve. We encourage FDA to reconsider this language encouraging sponsors to consider enriched clinical trials.

Expanded Access

MDA thanks FDA for the inclusion of expanded access within the draft guidance and supports the use of the FDA expanded access process (single-patient, small group, and large group) to deliver investigational therapies to patients ineligible for clinical trials and without other options.

With regard to such access, MDA urges the Agency to strengthen this section in the draft guidance while subsequently expanding efforts to facilitate the use of expanded access for patients in the NMD community as FDA does little in the guidance to encourage sponsors to utilize expanded access to deliver treatments to patients who cannot otherwise access the therapy.

We also encourage FDA to expand its current efforts on expanded access by more clearly communicating to sponsors the importance of offering expanded access programs to patients with unmet needs. MDA appreciates the significant efforts that the Agency has taken to streamline its approach to expanded access in the last several years by creating a new single-patient IND form (Form 3926), partnering with the Reagan Udall Foundation to create an expanded access navigator, and allowing an IRB representative to approve expanded access requests. We believe FDA could explore additional ways to lower the financial and regulatory hurdles sponsors face in offering their therapy through expanded access. FDA could also consider expanding the Oncology Center of Excellence's Project Facilitate model into neuromuscular diseases.

Partnerships with Patient Organizations

Finally, MDA thanks the Agency for emphasizing the importance of partnering with patient advocacy groups "to elicit their suggestions for the design of trials including trial protocols, that participants will be willing to enroll in and support."[21] The neuromuscular disease community is full of incredibly capable and regulatorily savvy patient organizations and advocates (including MDA). Sponsors should be forging partnerships with these organizations as soon as possible within their development program. We appreciate FDA's concurrence and emphasis on the importance of these partnerships.

We look forward to working with the Agency to ensure individuals with NMDs can fully participate within clinical trials. For questions regarding MDA or the above comments, please contact advocacy@mdausa.org.

[21] *Id.,* at 9

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs