July 31, 2020

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

Re: FDA-2020-N-0837-0001: Rare Disease Clinical Trial Networks; Request for Information and Comments

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 Request for Information (RFI) entitled, "Rare Disease Clinical Trial Networks; Request for Information and Comments". We are grateful for the Agency's efforts to innovate and accelerated rare disease therapeutic development.

The neuromuscular disease community served by MDA is comprised of over 43 individual rare neuromuscular disease populations, all of whom could potentially be included in a global clinical trials network considered by this RFI. While much progress has been achieved in NMD therapeutic development, many NMDs remain substantially underfunded. Furthermore, only eight neuromuscular diseases have an FDA-approved treatment, leaving the vast majority of NMDs without any approved therapy.

Consequently, we are excited about the prospects of an FDA-led global rare disease clinical trial network within FDA's Rare Disease Cures Accelerator program that could quicken the pace of NMD research and drug development, particularly for underfunded and under-researched rare NMDs. If constructed and financed appropriately, we believe such a network could bring impactful change to the NMD community. Furthermore, we encourage FDA to build upon existing efforts to create global clinical trial networks as several initiatives have already tackled many of the challenges discussed within this RFI. Given the potential impact this global clinical trials network could have on the neuromuscular disease community, we are pleased to provide responses to FDA's questions.

1. **What should be the immediate (<3 years) and long-term objectives of a global clinical trials network?**

Immediate Objectives: We have several recommendations for the Agency as it is considering both immediate and long-term objectives for a global clinical trials network. First, we recommend that FDA conduct a landscape analysis (of which this RFI is certainly a part) to conclusively determine what existing national and global clinical trial networks exist within rare

diseases. As FDA certainly understands, creating a duplicative effort where global clinical trial networks already exist may not be the best use of Agency time and resources.

Second, we recommend FDA completes a barriers assessment on why global clinical trial networks may not already exist in certain rare diseases. Reasons could include a lack of funding for a global clinical trial network, a lack of advanced scientific understanding and therapeutic targeting necessary to start a global clinical trial network, a lack of strong support and advocacy from an organized global patient community, and more. By identifying why global clinical trial networks may not already exist in rare diseases, the FDA can better target its expertise and resources to address the current challenges preventing global networks from being created.

Additionally, we encourage the FDA to commence efforts on the logistics of setting up a global clinical trials network. FDA can start by registering relevant sites and putting in place data and privacy agreements as well as setting IRB and governance structures. By tackling these logistical challenges early, FDA will be able to enroll patients as soon as the network is ready.

Finally, FDA should consider what harmonization of regulatory requirements may be necessary to allow for such a global clinical trials network to operate. Regulatory disharmonization could pose a major barrier to creating a well-functioning clinical trials network and should be addressed as soon as possible.

Long-term Objectives: In the long-term, MDA hopes that an FDA rare disease global clinical trials network could create economies of scale and address the market failures of our current global rare disease clinical trial system. Such a trial network could utilize a platform trial structure that permits interchangeable disease and drug permutations so that treatments can be tested as quickly as possible within patient populations that need treatments.

Furthermore, this global clinical trials network could utilize standardized endpoints and standard operating procedures (SOPs) that could substantially lessen the burden of coordinating clinical research. We believe a long-term goal of this network should be to substantially advance the use of standard data formats. If successful, this effort could be truly transformative in bringing new therapies to the neuromuscular disease patient population.

2. **How could a global clinical trials network for rare disease be organizationally structured (e.g., what mix of scientific and clinical disciplines are engaged to staff it; what process or guidance is followed for study protocol design; what standard procedures are employed for conduct of trials, and related protection of study participants and study data, etc.)? For example:**

    - **Are there experiences that can be shared regarding networks integrating a disease-specific development center with a disease-agnostic operations center?**

- **Are there experiences that can be shared regarding networks focused on a broad group of rare diseases and collaboration with regional or disease-specific networks?**

We have several recommendations for FDA on how best to organizationally structure a global clinical trials network. First and foremost, we urge the Agency to integrate patients and patient representatives into the governing body, advisory bodies, and any other facet of the effort that impacts the patient's experience in the network. The inclusion of patients and their representatives will ensure that their needs are met and may provide insights that improve the ultimate success of such a network.

Existing trial networks, such as the Rare Disease Clinical Research Network (RDCRN), can serve as examples to FDA as it is considering organizational structures. The RDCRN includes the Coalition of Patient Advocacy Groups (CPAG), of which MDA is a member, which is comprised of rare disease patient organizations that are integrally embedded in the clinical trials network.

We similarly advocate that leaders in developing rare disease natural history data registries are integrated into the effort to ensure the global clinical trials network can seamlessly (or as seamlessly as possible) plug into existing efforts, including FDA's, to develop longitudinal natural history data registries in rare diseases. This global clinical trial network could prove impactful in furthering the establishment of core data elements across registries through the use of a common data ontology. Furthermore, in addition to contributing to existing registries or setting up new registries in rare diseases without existing efforts, the network could also create a "registry of registries" for rare diseases that could serve as a central clearinghouse of rare disease registries. A global rare disease clinical trial network should seek to leverage existing, successful networks and registries rather than replace them.

3. **What kind of investigator experience is needed to start up and expand to implement a global clinical trial network (e.g., experience with clinical trial research administration, clinical trial operations, working with pharmaceutical companies in the design, conduct and management of clinical trials)?**

In addition to turning to patients and their organizations to provide expertise on ensuring the network is patient-friendly, we similarly recommend that FDA seeks investigator experiences from CROs, large academic centers, academic research organizations, and pharmaceutical companies who have conducted large global clinical trial networks. Each of these entities have either served as investigators, or worked closely with investigators, on successful global clinical trials and could be helpful to the Agency as it moves forward.

More specifically , we also encourage FDA to consult the expertise and experience of academic institutions such as the Duke Clinical Research Center and the Berman Center for Clinical Outcomes and Research as well as cooperative groups such as the Eastern Cooperative Oncology

Group (ECOG) and the American College of Radiology Imaging Network (ACRIN). Finally, we believe the Clinical Trials Transformation Initiative (CTTI) and TransCelerate BioPharma could each contribute important experiences. Each of these efforts can provide FDA with real-world experience in setting up clinical networks, and the challenges that may arise.

4. **What are successful models of governance for global clinical trial networks (e.g., role, responsibilities, and composition of various governing bodies)?**

There are several existing exemplary global clinical trial networks that we recommend the Agency consider as it is setting up governance structures for this effort. The Children's Oncology Group has over 200 institutions participating in a global clinical trials network and has successfully spurred clinical research in pediatric cancer. The Inherited Neuropathy Consortium, of which MDA is a supporter, has successfully brought together institutions across the United States, as well as centers in the United Kingdom, Italy, and Australia. Finally, the Cooperative International Neuromuscular Research Group (CINRG) has successfully brought together clinical sites from five continents to collaborate on clinical trials on Duchenne muscular dystrophy. Each of these three global clinical trial networks can serve as exemplary efforts for FDA as it is considering the governance structure of a global rare disease clinical trial network.

5. **What are potential opportunities to leverage and/or complement other existing networks (e.g., Institute for Advanced Clinical Trials for Children Network, Duke Clinical Research Institute Pediatric Trial Network, National Institutes of Health (NIH) Rare Diseases Clinical Research Network, NIH Experimental Therapeutics Clinical Trials Network, European Network of Paediatric Research at the European Medicines Agency)?**

MDA strongly recommends that the FDA works closely with the RDCRN, our nation's preeminent rare disease clinical trial network. The RDCRN already is a network of 20 rare disease consortiums that in aggregate conduct clinical research on over 200 rare diseases. Many of the consortium (including the aforementioned Inherited Neuropathy Consortium) include international clinical research sites. By collaborating with the RDCRN, the FDA can successfully build upon existing successful initiatives while further accelerating rare disease research through a focus on clinical trials. For example, one could imagine that sites that are already networked globally as part of an existing RDCRN could be more easily integrated into a single global network.

Finally, while not a clinical trial network, we encourage the FDA to partner closely with the International Rare Diseases Research Consortium (IRDRC). As an existing member of IRDRC, the FDA will be able to partner with international patient organizations, biopharmaceutical companies, research institutions, investigators, governmental organizations, and more. IRDRC is familiar with challenges in conducting international rare disease research and can be of great assistance to the Agency as it is constructing this network.

6. What infrastructure is required to startup, implement, and sustain a global clinical trials network (e.g., required administrative, financial and physical resources, centralized functions, data coordination and network operations, global interoperability)?

We recommend that the FDA consider several structures as it is creating and implementing a global clinical trials network. First, we recommend that FDA implement standard templates for participating IRBs to use for key elements of protocols and informed consent forms. We recommend the standardization of protocol feasibility contracts, training, quality management systems, and electronic data capture systems. If each of these core elements of conducting a clinical trial can be standardized, this network could run substantially more efficiently than otherwise possible.

In addition to these efforts of standardization, we recommend the creation of clinical coordinating centers and data coordinating centers for each region. While a central clinical coordinating center and data coordinating center may be inflexible, and individual centers burdensome, regional centers can provide the needed combination of flexibility and specificity.

With these structures in place, the global network will be able to become operational, fulfill local data requirements, and process data in an expedited manner.

8. What are the key milestones and associated timelines for starting up and expanding to implement a global clinical trials network?

As mentioned in an earlier answer, we believe that site agreements, IRB agreements, and standardized processes should be set up within the first couple of years as these structures will be integral to the long-term success of the network. Staffing and patient recruitment can commence in the several years thereafter to be fully prepared for therapeutic testing. Finally, once these steps are completed, we hope the first testing of therapeutics can occur within five years of the commencement of the effort at the very latest.

9. What are potential challenges or barriers to starting up, implementing, and sustaining a global rare disease clinical trials network?

We foresee a variety of challenges and barriers to starting up, implementing, and sustaining a global rare disease clinical trials network for which we encourage the FDA to prepare. First, we envision that disparate and conflicting privacy laws regarding personal health information (PHI), especially genetic PHI, across the world could pose challenges to administering a global clinical trials network. We encourage FDA to consider creating ways of structuring the network (especially through the use of regional clinical coordinating committees and data coordinating committees) to prevent such disparate rules from greatly inhibiting the success of the network. But first, FDA should analyze how current global clinical trials are managing these disparate approaches to PHI.

Second, disparate regulatory paradigms and bureaucratic approaches and timelines could delay the operation of the network, potentially for a damaging amount of time. We encourage the FDA to work closely with its regulatory partners in other jurisdictions to ensure such disparate approaches to do not hinder the network's operations or set up.

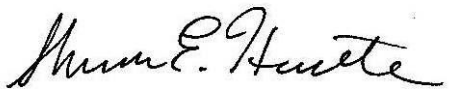
Third, ensuring sustainable funding for the network may prove challenging, especially considering the Rare Disease Cures Accelerator is currently funded by a time-limited appropriation from Congress. For such a network to succeed, sustainable, long-term funding must be guaranteed to attract global partners and ensure clinical trial success. We encourage the FDA to think creatively on how best to obtain long-term funding, either through an extended appropriation, or through the Prescription Drug User Fee program. Similarly, we encourage FDA to consider the extent of funding expected to come from partnering countries and jurisdictions.

Fourth, as is a challenge of all global clinical trials, standards of care may differ across clinical trial sites leading to potential variability in the results. This, of course, introduces noise into the data collected by the global network potentially compromising the success of the clinical trials. We recommend that FDA issue guidance and considerations for how best to employ a global approach but avoid location-derived variability in data collected. We encourage FDA to carefully examine how existing global clinical trials are successfully approaching this challenge.

Fifth, without patient and patient organization buy-in, a clinical trial may have recruitment and retainment challenges that could at best delay the trial's completion, and at worst undermine the success of the trial more generally. FDA should prioritize integrating patients and their organizations into the governance of the network to avoid such challenges.

In summary, we thank FDA for embarking on this herculean but potentially transformative challenge of setting up a global rare disease clinical trial network. MDA supports the FDA in this effort and hopes to contribute to the program's success in any way we can. For questions regarding MDA or the above comments, please contact Sharon Hesterlee, Executive Vice President and Chief Research Officer, at shesterlee@mdausa.org.

Sincerely,



Sharon Hesterlee, PhD
Executive Vice President, Chief Research Officer