March 15, 2021

Dr. Walter J. Koroshetz, Director
National Institute of Neurological Disorders and Stroke (NINDS)
6001 Executive Boulevard
Rockville, MD 20852

Re: NOT-NS-21-021: Request for Information on the 2021-2026 National Institute of Neurological Disorders and Stroke Strategic Plan

Dear Dr. Koroshetz,

In service of the neuromuscular disease (NMD) patient community, the Muscular Dystrophy Association (MDA) thanks the National Institute of Neurological Disorders and Stroke ("Institute" or NINDS) for the opportunity to comment on the Institute's Request for Information (RFI) on the "2021-2026 National Institute of Neurological Disorders and Stroke Strategic Plan" We are grateful for the Institute's continuing efforts to pursue and support innovative basic and translational research for the neuromuscular disease community

We are excited by the progress this draft strategic plan would represent and congratulate NINDS on putting together a comprehensive plan that could truly make a difference in the lives of the neuromuscular disease community. We are grateful to provide further considerations for NINDs as it continues to refine the strategic plan.

Seeing More Precisely - Biomarkers and Outcome Measures:

MDA is grateful for NINDS's inclusion of validated biomarker and outcome measure development within its strategic plan. The dearth of validated biomarkers and outcome measures in most neuromuscular diseases continues to hinder therapeutic development in neuromuscular diseases by limiting the drug development tools a therapeutic developer and the Food and Drug Administration (FDA) can utilize.

Other areas of medicine, particularly cancer, have seen incredibly acceleration in targeted therapeutic development largely because the science of biomarkers and outcome measures has advanced far enough to greatly simplify therapeutic development. Not only does this allow for therapies to better target the underlying causes of the disease, but it also allows for the therapy to advance through clinical testing and regulatory review at a quicker pace.

While certain neuromuscular diseases have biomarkers commonly used in drug development, such as Duchenne muscular dystrophy, the vast majority due not, including amyotrophic lateral sclerosis (ALS). Consequently, we applaud NINDS's emphasis on funding studies to develop biomarkers and outcome measures in neuromuscular diseases, and we agree this should remain a top priority for the Institute. We also ask the Institute to coordinate with the FDA on strategies

for investing in certain biomarker and outcome measure technologies to ensure NINDS is funding the most promising fit-for-purpose drug development tools in neuromuscular disease.

Improving Treatments:

First, we appreciate NINDS's focus on supporting preclinical development of targeted therapeutic interventions for the neuromuscular disease community. There are many potential impediments to developing safe and effective targeted therapies for neuromuscular diseases, including the rarity of the disease, the heterogeneity of the progression of the disease, and other economic and regulatory impediments.

Still, scientific understanding of the underpinnings of certain neuromuscular diseases continues to be the greatest impediment to therapeutic development. Consequently, we are grateful that NINDS continues to emphasize the importance of funding preclinical development of promising therapeutic interventions to further accelerate drug discovery and development.

Once again, we ask NINDS to coordinate with the FDA, the biopharmaceutical industry, and organizations such as MDA on prioritization of this funding to ensure all stakeholders in neuromuscular disease therapeutic development are coordinating their efforts.

Second, we are similarly excited by the NINDS Ultra-rare Gene-based Therapy (URGenT) Network. Cell and gene therapies are the future (and in some cases present) of neuromuscular disease treatments. We are supportive of this further emphasis that NINDS is placing on gene-based therapy development, particularly for ultra-rare diseases that may otherwise have trouble attracting research investments.

We would appreciate further information on how this effort intersects with the ongoing efforts in the National Center for Advancing Translational Sciences (NCATS) to accelerate gene-based therapeutic development in rare diseases. As a funder of gene-based therapy research in ultra-rare diseases ourselves, we are also interested in learning what collaborative opportunities exist to ensure our collective efforts complement, not contradict, or compete with, each other.

We also call for further conversation led by NINDS on the economic and regulatory impediments to delivering safe and effective gene-based therapies to the neuromuscular disease community. Often the basic and translational science behind a gene-based therapeutic intervention is not the impediment to bringing the therapy into the clinic and eventual approval. Instead, the very small patient population often make the financial investment and regulatory requirements untenable for private biopharmaceutical companies. Consequently, as efforts such as the NINDS URGenT Network launch, we believe the conversation on the economic and regulatory impediments to therapeutic development must accelerate as well.

Testing more precisely

MDA is supportive of NINDS's effort to advance natural history data collection as well as the establishment of common data elements within neurological diseases. These efforts are particularly critical in rare neuromuscular diseases where the natural progression of a

heterogeneous disease can be particularly understudied, and robust data collection efforts are sparse and siloed.

Consequently, MDA supports NINDS's common data element generation efforts. We similarly recommend that NINDS work closely with the FDA and other key stakeholders to ensure the common data elements established through this effort are relevant regulatorily and can be used within clinical trials and regulatory submissions. This is also critical as the collection of real-world evidence (RWE), patient experience data (PED), and patient preference information (PPI) only accelerates. We encourage NINDS to consider whether the common data element establishment effort would comply with CDISC standards.

We are also encouraged by the substantial number of common data elements within neuromuscular diseases included within this project, including many for ALS, Duchenne muscular dystrophy, and spinal muscular atrophy. There is still room to grow, however, as common data elements in Charcot-Marie Tooth, limb-girdle muscular dystrophy, and ultra-rare myopathies and myositises could still be considered.

Finally, given the growing number of efforts to collect natural history data in rare diseases, we once again emphasize the importance of collaborating closely with stakeholders to ensure efforts are not duplicative with NINDS's goals.

Advancing Health Equity and Diversity and Inclusion

We are pleased to see NINDS's emphasis on advancing health equity as a priority of NINDS research as well as fostering diversity and inclusion within the neurological research workforce. MDA shares both priorities and is eager to partner with NINDS on finding ways to further diversify the neurological research field as well as ensure societal inequities due to race, gender, and sexual orientation, among others, are successfully tackled within the neuromuscular disease community.

Consequently, ensuring NINDS-funded research reaches all individuals with neuromuscular diseases, and not just the privileged few, should remain on the forefront of NINDS strategic planning.

Rigor and Transparency

MDA supports NINDS's ongoing efforts to promote rigor in neurological disease scientific research. In July 2020, we submitted comments to NINDS on the Institute's "Request for Information (RFI) on Developing an Online Educational Resource for Training in the Principles of Rigorous Research". We are pleased to see these educational efforts continued as part of this strategic plan, and gratefully resubmit our suggestions for NINDS's consideration as it continues in these efforts.

As stated in our July 2020, comments, we support educational efforts that focus on good scientific practices, such as including the appropriate controls, ensuring proper power in the experiment, replication of any findings, and strict blinding. We support individualized training

for students at all levels, including hands-on training of undergraduates in the scientific method, and real-world lab training of graduate students on conducting experiments. NINDS-led webinars on these topics are authoritative and instructive, and online training must remain interactive to hold interest.

We encourage NINDS to remain focused on training the next generation of neuromuscular disease scientists and researchers through multi-model training offerings and are eager to assist in the dissemination of such resources to the scientific community.

Neuroethics

MDA supports NINDS's ongoing efforts in neuroethics and asks the Institute to direct resources to two ongoing, and growing, bioethical issues in neurological disease research. First, calls for avoiding placebo-controlled trials in neurodegenerative diseases as the science of historical, or other alternative, controls advances. Given the many issues surrounding the use of placebos, we request NINDS to consider adding further resources to this area.

Second, with gene and cell-based therapies continuing to advance in many neuromuscular disease patient populations, the bioethical issues associated with gene therapy testing and subsequent access are extensive. Consequently, we request NINDS to direct neuroethics resources towards the bioethical study of gene therapies in neuromuscular diseases.

Patient Engagement

We are pleased to provide recommendations to NINDS on how best to engage patients, their loved ones, and their advocates in NINDS opportunities. First, we commend NINDS for its existing efforts to engage the patient community through the annual NINDS Non-Profit Forum, and through ad-hoc workshops and conferences in which patients and their advocates can attend.

However, we have several suggestions for how NINDS can make their patient engagement efforts more robust. First, patients and their organizations are often limited in scope and ability by the amount of funding they can obtain. NINDS could consider ways to support patient advocacy organizations, especially those small patient advocacy organizations in the rare disease space, to participate in NINDS opportunities as well as contribute data and expertise to ongoing NINDS priorities.

Second, MDA believes that patients and their advocates can be more involved in the setting of NINDS grant priorities particularly within specific rare diseases. NINDS should first foster partnerships between the patient community and specific program officers responsible for their disease area, and then involve these patients and their organizations when prioritizing what to fund. Patient representatives could even be utilized to assist in the assessment and awarding of grants themselves much like the FDA Patient Representative Program facilitates patient experts to weigh in on the proprietary review of new drugs or biologics.

Third, we believe there should be greater opportunity for patient organizations to contribute to NINDS priorities. We are grateful for opportunities to comment on documents such as this

Strategic Plan, and we are similarly grateful for the opportunities to serve on the NANDS Council. Still, these opportunities are often anecdotal and do not allow for systemic input from multiple organizations across the neurological disease spectrum to contribute.

We hope NINDS considers our proposals to involve patients, their loved ones, and their advocates throughout the NINDS priority setting process as well as grant review and awarding.

In summary, we thank NINDS for offering us the opportunity to provide comments on the NINDS 2021-2026 Strategic Plan. MDA is a proud supporter of NINDS, and we hope to contribute to the Institute's success in any way we can. For questions regarding MDA or the above comments, please contact Paul Melmeyer, Director of Regulatory Affairs, at pmelmeyer@mdausa.org.

Sincerely,

Paul Melmeyer, MPP
Director of Regulatory Affairs