March 9, 2022

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

Re: FDA-2021-D-1214: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products – 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(MDA) thanks the Food and Drug Administration (FDA or "Agency") for the opportunity to comment on the Agency's Draft Guidance entitled, "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products – Guidance for Industry". We are grateful for the Agency's efforts to guide the stakeholder community on how best to utilize real-word data and real-world evidence to support regulatory decision-making.

MDA is the nation's leading nonprofit organization dedicated to transforming the lives of individuals living with 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, 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 research funding in the U.S. outside of the federal government.

To support the clinical, research, and drug development communities, MDA launched the neuroMuscular ObserVational Research Data Hub (MOVR). In our comments below, we will provide a brief history of MOVR, a discussion on how real-world data collected in MOVR can adhere to the recommendations put forward by the Agency in this Guidance, and our recommendations regarding the use of RWD and RWE in the regulatory decision-making process. We hope that the FDA considers these comments while finalizing this guidance.

MDA's neuroMuscular ObserVational Research Data Hub (MOVR)

About ten years ago, MDA recognized that there was a significant data shortage in the neuromuscular disease space and started crafting strategic approaches to accelerate data collection and its use by researchers, clinicians, and drug developers. One strategy that was identified was to leverage the MDA Care Center Network, which is comprised of over 150 care centers and 2,400 clinical providers across the United States, as a source for efficiently capturing

clinical data and growing a longitudinal dataset. Specifically, each year, over 90,000 medical visits are conducted and over 60,000 individuals living with a neuromuscular disease receive expert care at these centers. Capturing such a dataset would provide valuable knowledge on disease progression for drug development as well as for RWD and RWE in regulatory submissions and post-approval processes. This network also serves as a hub of neuromuscular research activity with over 20,000 individuals participating in clinical trials and natural history studies.

The US Neuromuscular Disease Registry (USNDR) served as MDA's pilot registry. The USNDR actively collected clinic-entered data across four diseases (amyotrophic lateral sclerosis [ALS], Becker muscular dystrophy [BMD], Duchenne muscular dystrophy [DMD], and spinal muscular atrophy [SMA]) at 26 care centers from 2013 to 2018. The success of USNDR, including collecting data from approximately 2,700 participants and using these data in an EU regulatory submission, inspired MDA to partner with IQVIA, a leader in human data science technology, to create MOVR. The USNDR dataset was directly rolled into MOVR, and three new diseases were added, including Facioscapulohumeral muscular dystrophy (FSHD), Limb-girdle muscular dystrophy (LGMD), and Pompe disease.

MOVR represents the first data hub that aggregates clinical and genetic data across multiple neuromuscular diseases. The core data elements captured across all diseases, include:

- Demographics – disease type, enrollment date, gender, DOB, race, ethnicity, insurance, education, and employment
- Diagnosis – date and age at diagnosis, clinical diagnosis, muscle biopsy, body regions first affected, family history, molecular and DNA results, and gross and developmental motor milestones
- Encounter – encounter date, height and weight, clinical trial participation, surgical history, falls and hospitalizations, medications, mobility, assistive devices, disease progression, spinal conditions and neuroimaging, nutritional and GI therapies, pulmonary and cardiology care, and multidisciplinary care
- Discontinuation – date of withdrawal, reason for study withdrawal, date of death, and cause of death

Data elements captured by MOVR were designed to capture critical functional and disease-specific outcome measures that have been identified by key opinion leaders, clinicians, and researchers as important to understanding disease mechanisms, tracking disease progression, and implementing standards of care. Most importantly, these data elements were not selected for a single study nor to benefit a particular study.

MOVR data are entered by clinical research staff from the information available in participants' medical records. Data are entered from the initial study enrollment visit through follow-up visits until the participant withdraws from the study, is lost to follow-up, or becomes deceased. The Encounter data is captured at each visit and is the foundation of the longitudinal dataset that could serve as RWD and RWE.

<u>MOVR's Current Data Landscape</u>

As of December 2021, 50 care centers are actively enrolling participants. These sites are classified as adult only, pediatric only, adult and pediatric, and ALS only care centers. The total number of MOVR participants across all sites is 4,222. Of these participants, 1,726 were enrolled directly into MOVR since 2019 while 2,496 participants consented to have their data migrated from the USNDR. A total of 894 participants are no longer actively participating in MOVR. Most of these participants were living with ALS who became deceased (n = 708) while others withdrew consent (n = 69) or were lost to follow-up (n = 72). The average number of encounters per participant ranges from 1.57 (FSHD) to 3.24 encounters (DMD) while the average number of months between the first and most recent encounter ranges from 11.51 (FSHD) to 26.53 months (DMD). Almost 90% of all electronic case report forms used to capture data into MOVR were marked complete, meaning all required data fields were filled for these forms. These data represent the start of a potential dataset for RWD and RWE used in regulatory submissions.

While MOVR serves primarily as a data hub, it may be used to assist with clinical trial matching as well as with clinical trial design and feasibility. Specifically, for clinical trial matching, a company may ask MDA to identify eligible participants in the MOVR data hub who meet its inclusion criteria. MDA then provides the clinical trial documentation to those MOVR Sites with individuals who were identified as potential candidates. Similarly, for clinical trial design and feasibility, MDA identifies the number of participants who would be eligible for a clinical trial based on the company's current trial design and performs additional analyses on how each exclusion factor affects the total number of participants who would be eligible. However, MDA does not support any sponsor who elects to use MOVR data in lieu of other data sources because specific outcome measures favor their regulatory submission.

Individuals living with neuromuscular diseases and their families are at the heart of MDA's mission. MOVR was created to ensure that these individuals are seen and counted and remain at the forefront of developing life-changing therapies. Therefore, MDA has implemented several safeguards to protect them.

MOVR Platform – Data captured on the MOVR Platform are managed by and hosted on IQVIA's Registry Platform (IRP). IRP holds high standards in managing and maintaining the System's Information Technology architecture in alignment with both the Health Insurance Portability and Accountability Act of 1996 and its implementing rules (HIPAA) and the 21 CFR part 11 to the extent applicable. IRP undergoes an annual independent HIPAA Risk Assessment and the Data Center where IRP is hosted undergoes an annual ISO 27001 assessment. Access to the MOVR Platform, which houses Protected Health Information (PHI), is restricted such that certain user roles are prevented from accessing data points. For example, clinical research staff at a MOVR site must attend a training session and be approved by the principal investigator at that MOVR site and by MOVR administrative staff before accessing the MOVR Platform. Once access is granted, approved individuals can only view data captured by their site. User access is reviewed monthly.

IRB Approval – MOVR Sites must obtain institutional review board approval of MOVR's study protocol before enrolling participants and accessing the MOVR Platform. Additionally, written informed consent and assent, as appropriate, from each MOVR participant and/or their legal guardians is required before their data can be captured in MOVR.

Data Access and Use – Access to and use of MOVR data are managed by a Data Governance Policy that covers several key areas, including an overview of MDA's roles and responsibilities, authorized and non-authorized data use, data ownership, and publication rights and requirements. This policy must be reviewed and signed before a Data Request Form can be completed. Data requests are reviewed by MOVR administrative staff. Requests that may fall outside of the data use policies outlined in the Data Governance Policy are reviewed by the MOVR Research Advisory Committee, which is comprised of clinicians, researchers, and MDA stakeholders. Once a data request is approved, aggregate data is de-identified. To de-identify MOVR data, a Re-identification Risk Determination is conducted to review and assess the re-identification risk of the requested dataset. De-identification standards used for this evaluation are consistent with the HIPAA Privacy Rule's Expert Determination standard. This determination stipulates changes that are required to reduce the re-identification risk, which are then implemented to create a non-identifiable dataset. Most importantly, the Data Governance Policy only allows the presentation of MOVR data in the de-identified aggregate form. Presenting patient level data is strictly prohibited to further prevent the risk of re-identification.

Discussion and Requests for Clarifications

MDA is grateful for the FDA providing this draft guidance as it allows us to thoroughly review MOVR, including its policies and procedures, data systems and standards, and data use. However, there are two main concerns about the guidance that we would like to discuss: (1) the roles and responsibilities of the sponsor and (2) the submission of patient-level data.

<u>The Roles and Responsibilities of the Sponsor</u>
MDA is well-aware of the time required to prepare an application for regulatory submission. MDA is working diligently with biotech and pharma partners to assist their drug development pipelines and accelerate the pre- and post-approval processes. The roles and responsibilities detailed in this draft guidance are extensive for a sponsor, and MDA is concerned about how these could impact the time to market for effective therapies.

The guidance is written as if the sponsor is the sole operator of data collection, transformation, analysis, and interpretation of the RWD it is submitting and/or intending to submit. If the guidance is encouraging sponsors to create registries to satisfy the proposed requirements of the RWE Program (and have peace-of-mind that RWD meets these requirements), this could add substantially to the cost and timeframe for therapy development. In the neuromuscular disease community, building a new registry or dataset for each therapy could be extremely detrimental as it siloes patient data, creates redundancies, and increases potential conflicts of interest[1,2]. However, if the guidance is encouraging sponsors to utilize existing registries, many of the roles and responsibilities listed for the sponsor should be transferred to the owner of the registry as it

[1] Hesterlee S. "Chapter 8: Optimizing Rare Disease Registries and Natural History Studies." *Rare Disease Drug Development – Clinical, Scientific, Patient, and Caregiver Perspectives*, edited by Raymond A. Huml, Springer, 2021, 109 – 125.
[2] Hollak CEM, Sirrs S, van den Berg S, van der Wel V, Langeveld M, et al. (2020). Registries for orphan drugs: generating evidence or marketing tools? *Orphanet Journal of Rare Diseases*, 15:235.

is likely that the registry is currently fulfilling these responsibilities. Therefore, the registry may need to play a larger role in the submission process than what is described in this draft guidance.

First, the sponsor is responsible for documenting how the data satisfies the proposed guidelines for RWD and providing source data for verification. Based on the MOVR Data Governance Policy, the sponsor would not have access to the source data and therefore, MOVR would take responsibility for the source data verification. Currently, MOVR is preparing strategic plans for a RWD audit to demonstrate how it satisfies the guidelines proposed by the recent draft guidances released by the FDA, particularly the draft guidance entitled "Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products". Under our current approach, it would be preferrable that MOVR works directly with the FDA to provide required documents rather than providing such documents to an intermediary sponsor who then transmits them to the FDA. Providing source data to a sponsor who then provides it to the FDA requires an extra step and could put PHI at risk. We believe that to minimize this risk, the FDA could consider working directly with the MDA and its MOVR Sites to secure these source data.

Second, according to the draft guidance, the sponsor is responsible for providing training to site personnel and actively monitoring data accrual and processing. Currently, MOVR administrative staff provide extensive training and communicate with site personnel to monitor data accrual. Additionally, MOVR administrative staff meet bi-weekly with IQVIA – the data collection and management platform host – to discuss data management and processing. Do MOVR Sites need to undergo additional training led by the sponsor to satisfy FDA requirements? If each time a new sponsor is submitting data, would this require each sponsor to provide training? The roles and responsibilities of the sponsor need to be refined while the roles and responsibilities of the registry need be defined for the regulatory submission process. MDA recommends that the FDA creates a certification or qualification program for registries that streamlines assessing registry data as a compliant source of RWD. Further discussion on this proposal is below.

<u>The Submission of Patient Level Data</u>
As detailed above, MOVR is extremely strict when it comes to protecting participant data and PHI. As the guidance currently reads, the sponsor must have the ability to submit patient level data from MOVR. However, the guidance does not clearly define what patient level data this would entail. If patient level data is submitted as de-identified data, who is responsible for the risk of re-identification? Neuromuscular diseases are rare diseases and therefore, the ability to re-identify data is significantly higher compared to other disease types. We urge the FDA to clarify what patient level data includes and the format in which it should be submitted.

Recommendations for the FDA

The rare neuromuscular disease community is experiencing a surge in therapeutic development, including disease-modifying therapies. Nearly 200 products are in the therapeutic pipeline for neuromuscular diseases, with almost half of these products at preclinical versus clinical stages of development. Between 2013 and 2018, the number of products in clinical trials for neuromuscular diseases increased fivefold, from around 20 to 100. In total, over fifteen products are approved by FDA for a rare neuromuscular disease.

MDA is highly aware of the time and financial burdens of the regulatory submission process for the sponsor, the FDA, and any other organization providing data or viewpoints for FDA to consider. Reducing these burdens would greatly benefit all parties. Consequently, we are eager to find ways to lower the time and financial burdens on sponsors when submitting RWE to FDA as part of a regulatory submission.

One such way to reduce this burden is to create a certification or qualification program that registries can complete to demonstrate that they are FDA-compliant and a reputable source for RWD. This qualification program could allow for registries to prove compliance with the recommendations put forward by the Agency in this guidance and the other draft guidances issued under the RWE Program without having to reassert compliance with every product submission, thus greatly reducing the resources needed for both the sponsor and the FDA.

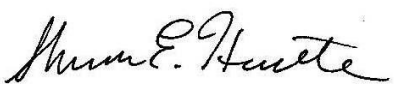
A qualification program would allow a registry to prepare standardized documents to help sponsors with the submission process and the FDA can be confident in the integrity of the data being submitted. Therefore, upon inclusion of a registry's data in an application, the FDA would see that the registry has already satisfied all requirements and the focus can be on the data included rather than the processes and procedures used to collect, store, and transform the data.

This qualification program can join the existing drug development tool qualification programs as efforts that streamline and reduce the resources needed to use innovative approaches to therapeutic development and regulatory decision-making. Already the animal model qualification program, the biomarker qualification program, and the clinical outcome assessment qualification program are working towards these goals. A registry qualification program could similarly transform therapeutic development efforts, particularly in rare neuromuscular diseases.

In conclusion, MDA created MOVR to improve health outcomes and accelerate drug development. MOVR's foundational goals are to understand the course of disease, increase access to clinical data, speed up clinical trial recruitment, and predict disease progression. The MDA is committed to growing MOVR as a resource to support study and trial feasibility and design and as a data hub for post-approval follow-up studies. By leveraging MDA's strong, historical relationships in the medical, scientific, and patient communities, and utilizing the data platform to capture clinical data from visits happening already, MOVR is poised to overcome the current challenge of industry-wide data shortages in rare diseases with a unique level of stability and scalability.

We are grateful for the opportunity to comment on FDA's efforts to expand the use of real-world data in regulatory decision making. For questions regarding MDA or the above comments, please contact Paul Melmeyer at 202-253-2980 or pmelmeyer@mdausa.org.

Sincerely,



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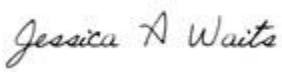

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