



August 1, 2023

Patrizia Cavazzoni, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10001 New Hampshire Ave
Silver Spring, MD 20903

Re: Docket No. FDA-2022-D-2870 for “Decentralized Clinical Trials for Drugs, Biological Products, and Devices”

Dear Dr. Cavazzoni,

On behalf of the more than 25 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency’s draft guidance, “Decentralized Clinical Trials for Drugs, Biological Products, and Devices.”

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective therapies.

For a number of reasons, clinical trials are particularly difficult to conduct for rare diseases. For instance, the often small and geographically dispersed patient populations make enrollment for rare disease trials disproportionately time consuming and resource intensive. Far too often, rare disease patients must travel long distances to participate in clinical trials and face financial barriers, which can negatively impact trial recruitment and retention, and further complicate diversity efforts as patients from historically underserved communities tend to be disproportionately impacted by these challenges. As the experience during the COVID-19 pandemic has shown, decentralized trials can make trial participation faster, easier, and more equitable.

Over 95% of the more than 7,000 known rare diseases do not have an FDA approved treatment, making access to clinical trials even more essential for rare disease patients that usually lack other treatment options. More representative clinical trials that better reflect the whole patient populations are also vital to building trust among historically marginalized parts of the patient population. Moreover, they are vital for ensuring the developed therapies are indeed safe and effective for the whole patient population for which the therapy is labeled. In fact, data showing different safety or efficacy profiles across subparts of the patient population can hold vital clues about the disease and lead to new therapeutic breakthroughs. Clinical trials have historically not been representative of the entire community, and as rare diseases can

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affect each person differently, there are knowledge gaps regarding how they appear in minority populations.¹ By conducting decentralized clinical trials and ultimately increasing diversity efforts, more data can be collected, resulting in more comprehensive treatments for those living with rare diseases.

For these reasons, ensuring that clinical trials are accessible, flexible, and meet rare disease individuals where they are is a priority for NORD. NORD thanks the Agency for drafting this guidance to help drug sponsors expand their reach in clinical trials and to help make trial participation easier and more equitable, especially for rare disease patients.

NORD is pleased to offer specific recommendations below for how to maximize the impact of this draft guidance, informed by our 40 years of experience working constructively with all key stakeholders to help bring more rare disease therapies to more patients more quickly.

Recommendation 1: Provide additional guidance to help rare disease drug sponsors leverage decentralized trials to improve trial enrollment and retention

Challenges with trial enrollment and/or retention are among the key reasons rare disease trials fall behind schedule or ultimately fail to generate sufficient scientific evidence. Far too often, rare disease patients are required to travel long distances to access clinical trials, most of which are conducted in large academic research centers. These often-significant travel distances are one of the enrollment challenges in rare disease trials as many participants cannot commit to the entirety of the clinical trial, ultimately making it difficult to produce meaningful results.² During the COVID-19 pandemic, decentralized trial practices were adopted to continue drug development despite the challenges posed by COVID-19 restrictions. These innovative clinical trials reduced the need for trial participants to physically visit trial sites by providing adaptive practices to meet individuals in their own communities.

NORD supports FDA's efforts through this draft guidance to make some of the success made possible through the flexibilities of the COVID-19 era permanent. Specifically, we appreciate that the guidance outlines various mechanisms to make it easier for drug sponsors to deliver drugs to a patient's home, enlist local healthcare providers to support parts of the trial, and to incorporate some remote monitoring through telemedicine visits, all without jeopardizing the scientific rigor of the trial. These adaptations will reduce the need for in-person visits to the trial site and can have a significant, positive impact on trial participation. However, given the medical complexity of many rare diseases and the exceedingly small sample sizes, which magnify the impact of each minor data challenge, more guidance specific to rare diseases and small-population trials is needed to ensure the safety and quality of these trials for rare disease patients. Drug sponsors, local health providers, academic experts with extensive experience supporting rare disease patients, and patient groups should closely collaborate to ensure the trial design meets the unique needs of the population being studied while ensuring sufficient rigor of in the study design, data provenance, and endpoint selection.³ Specifically, we urge FDA to provide additional

¹ U.S. Department of Health and Human Services. (2023, April 24). *Diversity and inclusion in clinical trials*. National Institute of Minority Health and Health Disparities. <https://www.nimhd.nih.gov/resources/understanding-health-disparities/diversity-and-inclusion-in-clinical-trials.html#:~:text=People%20may%20experience%20the%20same,can%20benefit%20from%20scientific%20advances>.

² Ghadessi, M., Di, J., Wang, C. et al. Decentralized clinical trials and rare diseases: a Drug Information Association Innovative Design Scientific Working Group (DIA-IDSWG) perspective. *Orphanet J Rare Dis* 18, 79 (2023). <https://doi.org/10.1186/s13023-023-02693-7>

³ *Id.*

guidance on the following two issues which we believe will be key to ensuring decentralized trials will truly work for rare disease patients.

Additional guidance, best practices, and lessons learned will ensure decentralized trials meet the community's needs. To demonstrate the feasibility of remote participation in clinical trials, and to show how this approach can help reduce participants' burden associated with clinical site visits, NORD has for the past three years participated in an FDA-funded study of remote study engagement and data collection. The pilot History of Metachromatic Leukodystrophy (HOME) study adopted a site-less participation approach to reduce the burden on caregivers and patients related to accessing clinical trials. By using innovative technologies that allow for video assessments and the accessibility to the Survey of Health and Patient Experience (SHAPE) platform on smart devices, researchers demonstrated the feasibility of clinical trials in remote settings and that ease of access to technologies reduced caregivers and patients of the burdens associated with centralized clinical trials.⁴ However, sufficient patient and caregiver education and support were needed to ensure consistent, high-quality data collection. User-friendliness and a carefully designed user experience were vital to ensuring rare disease patients had access to potentially life-saving therapies in the comfort of their own homes. A clear understanding of the community's needs and trusted partnerships throughout the study were vital to conveying the value in conducting decentralized clinical trials that use versatile technologies.

Based on these experiences, NORD recommends FDA work with patient groups, drug sponsors, and other key stakeholders to create additional guidance, best practices, and lessons-learned workshops to give additional support in ensuring decentralized trials truly meet the needs of the community – including individuals navigating unique physical, geographic, or psychosocial access challenges.

Additional guidance is needed to ensure local healthcare providers can be effective partners in the trials. In designing the trial, drug sponsors need to consider the severity and complexity of the condition and the surrounding resources in the population to determine how the decentralized trial can be designed to retain quality care and endpoint assessments.⁵ Local providers provide more accessible avenues to trial participation such as reducing the need to travel for diagnostic bloodwork or imaging services. Also, primary care providers in their communities tend to be particularly well-suited to providing local, culturally appropriate care. However, as more local providers are asked to support their patient's engagement in clinical trials, providers need additional outreach, support and education to ensure consistent trial support without negative impacts on the other services they provide to their patient participating in the clinical trial.

This recommendation is supported by extensive experience with NORD's Rare Disease Centers of Excellence. These centers are a unique network of 40 academic medical centers, children's hospitals, clinics, and institutions with the shared goal of advancing care and expanding access for rare disease patients. NORD and our Centers of Excellence share a core goal of bringing appropriate care closer to the patient's home. Through collaboration and knowledge sharing, the network aims to create a scalable model of treatment and research for all rare diseases that would otherwise be unattainable, providing a much-needed national infrastructure to help accelerate advancements in rare disease diagnosis, treatment, and research. By offering vital connections, education, and opportunities for shared learning among participating providers, the network will enable more rare disease patients with opportunities to seek care

⁴ National Organization for Rare Disorders, Danbury, CT, U.S.A.

⁵ *Id.*

(and ultimately enroll in clinical trials) closer to their homes, including serving the needs of patients from all backgrounds. These centers will be more adept to the needs of rare disease patients by having access to new innovations and technologies to aid in treatments and diagnoses across the network and reach into community care including through primary care and urgent care settings. The opportunities for peer mentoring and support have been among the most valuable aspects of this network.

Based on these experiences, FDA should provide additional guidance and best practices for drug sponsors on creating partnerships with health clinics and other local healthcare providers that will be involved in decentralized clinical trials, with an emphasis on rare disease trials where local providers are unlikely to have seen similar cases before. As the draft guidance noted, decentralized trials can take place in settings where traditional trials are not often held, either with local healthcare providers, at the participants' homes, or via telehealth services.⁶ Given the use of new technologies and coordination with local providers, sponsors should be given best practices to follow to ensure proper management, health protocols, and safety considerations can be mitigated to ensure reliable data is collected during the trial.

Recommendation 2: Provide additional guidance to help sponsors leverage decentralized trials to meet trial diversity goals and ensure clinical trials accurately represent the whole patient population

Ensuring that clinical trials appropriately represent the intended patient populations is a priority for NORD and we thank the FDA Commissioner, Dr. Califf, for acknowledging how decentralization will provide easier trial access for a more diverse population.⁷

Patients from historically underserved populations are consistently underrepresented in clinical trials, to the detriment of everyone involved. Broadly, clinical trial participation for the Latino/Hispanic population in the United States remains low at 11%, despite constituting 18% of the population in the United States.⁸ Increasing access to a more diverse population is a particularly critically important issue for rare diseases given the limited patient populations, geographic dispersion, and heterogenous disease manifestation. For instance, in a recent study published by the Foundation for Sarcoidosis Research, researchers found that in the analyzed rare disease trials, Black participants constituted only 9% of clinical trial participants, whereas white participants constituted 70% of participants.⁹ In the case of sarcoidosis, Black women in particular are three times more likely to receive a sarcoidosis diagnosis in their lifetimes with mortality rates 12 times higher than those of white patients with sarcoidosis.¹⁰ Despite having more diagnoses and

⁶ Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, & Oncology Center of Excellence. (2023, May). Decentralized Clinical Trials for Drugs, Biological Products, and Devices. U.S. Food and Drug Administration. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices>

⁷ Office of the Commissioner. (2023). *FDA takes additional steps to advance decentralized clinical trials*. U.S. Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-takes-additional-steps-advance-decentralized-clinical-trials>

⁸ Day, J. A. (2023, May 1). *Why it's vital that all people - including people of color - take part in Clinical Research Studies: Johns Hopkins Division of Gastroenterology and Hepatology*. Johns Hopkins Medicine. <https://www.hopkinsmedicine.org/research/understanding-clinical-trials/poc-and-clinical-trials.html>

⁹ Foundation for Sarcoidosis Research. (2023). *Advancing clinical trial equity for black patients with sarcoidosis*. Foundation for Sarcoidosis Research. <https://www.stopsarcoidosis.org/wp-content/uploads/FSR-Clinical-Trial-Diversity-White-Paper-FINAL.pdf>

¹⁰ *Id.*

worse outcomes, sarcoidosis drugs are being produced from trials that are not representative of its patient population.¹¹

Many disparities hinder the participation of historically underserved populations in clinical trials, including mistrust in clinical research and financial and logistical barriers to participation. Research has shown that historically underserved populations are more likely to participate in clinical trials if they:

- Are asked to participate in the trial by a trusted healthcare provider or community leader;
- Are given information on how the trial benefits them or their community;
- Receive support for clinical trial participation, including financial support to cover travel expenses and lodging, and flexible appointment times to minimize disruptions to work and caregiving obligations; and/or
- Hear the experiences of other patients who are part of the clinical trial.¹²

Equitable access to clinical trials and equitable enrollment of trial participants from historically underserved communities requires deliberate planning and strong community partnerships to achieve. Sponsors will require additional guidance and support to ensure historically underserved communities, patients with disabilities, and patients without access to broadband have equitable access to decentralized trials, and that the flexibilities afforded by FDA's decentralized trials guidelines indeed increase trial diversity. Experiences from the NORD Rare Disease Centers of Excellence program again point to the importance of community ties and multi-sector partnerships. Many of the centers already have extensive community ties and bring decades of experience and programs devoted to reaching out to medically underserved communities in their region, including:

- Communities of color, both urban and rural, may have a strong mistrust of clinical research due to unethical medical research;
- Immigrant communities who face a variety of cultural, linguistic, and economic barriers, challenges accessing health care coverage, as well as potential mistrust of law enforcement and government agencies; and/or
- Rural communities with limited broadband access to health care facilities or public transportation.

While having clinical trials in a decentralized manner is an effective way to bring the trials into communities, efforts should be put in place to ensure that potential participants are made aware of the trials and their benefits, given financial support, and reach participants with language barriers.

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around decentralized clinical trials, as well as other strategies to bring safe and effective rare disease drugs quickly and effectively to market. For questions regarding NORD or the above comments, please contact Hayley Mason, Policy Analyst, at hmason@rarediseases.org

Sincerely,



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¹¹ *Id.*

¹² *Id.*