



July 31, 2020

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2020-N-0837 for “Rare Disease Clinical Trial Networks; Request for Information and Comments”

Dear Sir or Madam:

The National Organization for Rare Disorders (NORD) is grateful for the opportunity to submit these comments to the Food and Drug Administration (FDA or the Agency) regarding the third component of the Agency’s Rare Disease Cures Accelerator (RDCA) – improving the design, conduct, and completion of rare disease clinical trials. As a key collaborative partner in the RDCA and a developer of a patient registry and natural history study platform for rare diseases that is frequently leveraged in the development of clinical trials, NORD is uniquely positioned and stands willing to provide FDA with insights as to the startup, implementation, and maintenance of clinical trials networks for rare diseases.

Since 1983, NORD has been an independent advocacy organization dedicated to patients and families affected by rare diseases and the organizations that serve them. NORD, along with its more than 300 patient organization members, is committed to the identification, treatment and cure of the more than 7,000 rare diseases, of which approximately 90% are still without an FDA-approved treatment or therapy. We continue to be supportive of the RDCA, having served an integral role in the first two components of this valuable initiative since its inception, and we appreciate the opportunity to provide our perspective on component three.

NORD has been privileged to be involved in the establishment as a chosen partner of the RDCA since its outset. This ambitious program has been touted by the Agency as having the potential to revolutionize rare disease drug development and review. Janet Woodcock, head of CDER, has said of the RDCA, “This is the best we can do. If we can pull this off it truly will accelerate cures of rare diseases.”¹ Dr. Woodcock has been a longtime advocate of the need for longitudinal natural history data for rare diseases and the RDCA creates a centralized database to harmonize and standardize data sources and goes even further to provide the tools to support advanced analytics, standard outcome measures, and a coordinated clinical trial network.

¹ NORD, FDA Hope New Data Platform Leads To New Rare Disease Cures, Inside Health Policy, 9/17/19

A. Background on the RDCA Framework and Insights from Other Components of the Program

Upon recognizing the need for greater collaboration among rare disease patients, researchers, and drug developers, FDA developed and launched the RDCA to create the infrastructure for a more cooperative scientific approach. This program was born out of the recognition by those at the FDA that rare disease drug development is fraught with challenges that have been hard to address. The vast knowledge gaps that exist about the natural course of most rare diseases coupled with small non localized patient populations are challenging barriers to overcome. The proposed solutions via the RDCA to develop standard measures to inform high quality and reliable data collection, and to centralize and make accessible data sources to advance rare disease characterization, aims to be instrumental in revolutionizing the conduct of clinical trials for rare diseases.

With over 7,000 known rare diseases and more being discovered each year, the need for further knowledge is paramount. The critically important role of natural history studies to characterize rare diseases, paired with additional data types including clinical trials, patient registries, electronic health records, and genomic data, became an obvious starting place for the RDCA program. Once a disease has been characterized, it becomes important to measure how a patient, as FDA puts it, feels, functions, or survives.² These patient perspectives are used to help create core clinical outcome assessments and inform endpoints for clinical trials, which is the second component of the RDCA program. The final component of the RDCA program seeks to build a rare disease clinical trial network which can be revolutionary for rare disease patients around the world in its ability to expedite drug development for rare conditions and have practical applications for populations larger than those in rare disease trials. NORD commends FDA for recognizing that the RDCA program should be treated as an ecosystem that sets up each component to be interconnected with and to inform the development of the others. NORD also hopes that the agency will continue to leverage and rely upon NORD as an organization and trusted partner for each component of the RDCA as they develop and evolve.

The following components make up the RDCA and were identified as key to facilitating a cooperative approach:

1. Providing a centralized standardized infrastructure to support and accelerate rare disease characterization.
2. Developing standard core sets of clinical outcome assessments and endpoints that are relevant to rare conditions and that are meaningful to the patients who are afflicted by these conditions.
3. Creating a global rare disease clinical trials network to support the conduct of clinical trials in rare disease populations.³

² Clinical Outcome Assessment (COA): Frequently Asked Questions

³ Food & Drug Admin., Rare Disease Cures Accelerator, <https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator>.

Component 1: Rare Disease Characterization

Through a cooperative agreement funded by a grant from the FDA, NORD and the Critical Path Institute (C-Path) formally launched the development of the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) in September 2019 with the goal of providing a centralized and standardized infrastructure to advance the first RDCA component. The purpose of RDCA-DAP is to integrate rare disease data from a variety of sources, (including natural history studies, clinical trials, and patient registries) into a robust analytical platform that will promote the sharing of patient-level data, encourage the standardization of data collection, and allow access to the data by researchers to foster a better understanding of a given rare disease and its progression in order to inform clinical trial design and regulatory review.

Our participation in the RDCA-DAP project has reinforced a core principle of NORD's: incorporating input from the patient community is critical at every step of the process. People with rare diseases, families, caregivers, and the organizations that support them are experts in their particular disease. Based on their experience of living with the disease, patient groups have significant insights to share about the natural history of their disease, including symptoms, disease progression, and the effect of available treatments. They also have important contributions to make to benefit/risk analysis, which is especially valuable in the areas of unmet medical need. Further, patient advocacy groups are agile and are willing to share information about their disease to help other patients and to advance scientific understanding and clinical development.

A particularly novel and innovative aspect of this component is the availability of an advanced analytics platform which will, using available data, allow researchers to simulate clinical trial designs toward refining the duration, study population, sample size, and endpoint selection driving efficiencies in resources and informing the acceleration of rare disease drug development timelines. Over time, the value of this advanced analytics platform will increase exponentially as the volume and quality of the available data grows, we incorporate the learnings from the modeling exercises into future iterations of the platform, and share lessons learned and best practices with community stakeholders along the way.

Component 2: Clinical Outcome Assessments

NORD and C-Path are also collaborating on a second FDA-funded cooperative agreement, which establishes a Rare Disease Clinical Outcome Assessment (COA) Consortium in furtherance of the second RDCA component. Developing a COA that is fit-for-purpose for its intended use in drug development can be a lengthy and costly process. The goal of this consortium is to create a publicly available reference source of information on COAs to encourage standardization in data collection and clinical trial endpoints, reduce the need for de novo measure development, and support the adaptation, where applicable, of existing COAs for new use cases and across multiple diseases populations, all in an effort to expedite the drug development process. In addition to this work with C-Path on COAs, NORD is also partnering with the Northwestern Clinical Outcome Assessment Team (NUCOAT) on an initiative to

develop a core outcome set of COAs on physical function for use across a set of common and rare diseases.

These projects have demonstrated not only the power of individual patient engagement, but also the value of NORD's Membership, Corporate Council and IAMRARE Registry Program. For the project with C-Path, NORD doubled engagement in the planning committee for the Rare Disease COA Consortium by leveraging relationships with our Corporate Council members. For the project with Northwestern, through working with our 300+ non-profit organizational Membership and NORD's IAMRARE Registry Program, we have led recruitment efforts for the incorporation of patient perspectives into the development of COAs. This rare disease research, remarkably, has not been slowed by COVID-19, when so much scientific progress has been paused or challenged. Rather, the process has demonstrated to the project teams the value of leveraging multi-stakeholder relationships and remote research participation.

B. Collaboration Among All Stakeholders Is Critical to the Success of the Clinical Trials Network Component

To enhance FDA's efforts to implement the third RDCA component, it has requested feedback from stakeholders about how to approach the startup and implementation of global clinical trial networks for a range of rare diseases.

While the three components of the RDCA program are separate initiatives, their goals are complementary, and the components were intended to be integral pieces of an overall system designed to serve the unmet needs of patients with rare diseases.

NORD sees the work to characterize rare diseases as critical to informing the creation of COAs and meaningful endpoints which both feed into the larger goal of creating more efficient and effectively designed clinical trials to accelerate rare disease drug development. This is foundational work for the development and design of a clinical trial network, which could provide an optimized application for the curated resources on fit-for-purpose COAs for rare diseases, and then new data from trials may be shared back with RDCA-DAP and so on; in this way all the components can inform and support the others, with the sum of the parts leading to greater impact and more quickly than any one component of the RDCA program would achieve on its own

NORD is supportive of the clinical trials network initiative and appreciates the enormous benefit that a global network would provide to patients of rare diseases. There is a wide divergence of laws and regulations surrounding clinical trial conduct, data collection, privacy, and other relevant areas across various countries – all of which add to the complexity of the project and risk that the project's goals will not be achieved.

Understanding the needs of all stakeholders – patients and families, researchers, industry, regulators – and where the themes converge and diverge will provide important information for reflection as the global clinical trials network is established. Careful and thoughtful design of the rare disease global clinical trials network to ensure that plans, processes, procedures, policies,

budgets, governance, and participation account for the intentional inclusion of diverse racial and ethnic populations in clinical trials is imperative.

Careful strategic planning is necessary not only to create an integrated ecosystem, but also to develop the fundamental points that will drive the ultimate usability of the program. First, a clear articulation and understanding of the value of the initiative is critical to obtaining support from the public. To ensure robust participation, stakeholders will expect answers to basic questions that explain why this resource is so important and what the expected value will be to each stakeholder group. It will also be critical to ensure there are sufficient mechanisms for engagement and involvement in the RDCA initiative, as well as making clear the requirements and accountability measures needed for participation. Details around why and for what benefit stakeholders should entertain shifting their operations in order to participate will be important to articulate. Setting parameters surrounding access to data and expertise will need to be established. And clear goals and outcome measures should be set forth at the outset.

C. Responses to Selected Questions

Summarized below are NORD's responses to selected questions that FDA posed in its Request for Information.

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

The long term goals of a rare disease global trials network should include the contribution to trial designs that help to overcome some of the challenges facing rare disease research and treatment development, increased success rates of clinical trials and the speed in which safe and effective therapies are made available to patients, and increased collaboration among community stakeholders, including the private sector, thereby breaking down the silos of activity currently taking place in rare disease research. Measurable improvements and benefits such as these are critical to the long term, overarching success of the program as they ensure that engagement and support remain high – key factors in developing a sustainable network.

Given the ambitious nature of the project, it will be important to come to consensus on the short- and long-term goals of the trial network and then identify the objectives critical to achieving those goals, including timeframes, activity co-dependencies, and resources requirements. More immediate objectives should focus on establishing the foundational elements of the program as they will serve to support future goals and objectives and can also play a pivotal role in the network's sustainability. Foundational elements should include, (but not limited to), establishing the network's governing framework, its operational structure, stakeholder engagement, and integration with RDCA-DAP and COA program activities.

A robust landscape analysis of existing research and clinical trial networks would be a practical means of providing valuable input to the development of those foundational elements. In addition to informing the design of the RDCA global clinical trial network, existing networks may be further leveraged by serving as members of the RDCA network.

Another immediate objective should include developing pilot projects that could be used to test out aspects of the trial network framework as it is being developed and establish early successes. Given the program's complexity, early learnings from pilot projects support an agile, iterative approach to developing the network over time and take into consideration the learnings that will come from working with diverse characteristics of the global rare disease ecosystem.

We believe that achieving global collaboration on a clinical trials network would likely be more attainable once we take the first step to implement the network and infrastructure on a national scale. In the immediate term, our focus should be on developing a small core network that leverages the information gained from the first two components of the RDCA, piloting and establishing the cohesive coordinated ecosystem. As our experience and processes evolve, we can expand the network accordingly to achieve the vision of a global network. One approach may be to collaborate with other international entities, such as the International Rare Diseases Research Consortium (IRDiRC) and Rare Diseases International (RDI), to devise an international framework that can be leveraged to support interoperability across countries with varying degrees of legal and regulatory complexity.

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?

Establishing a rare disease patient governing board that can be engaged early to identify goals, objectives, and priorities will be critical. In addition, designing for patient input at all levels of the global clinical trials network, including in study protocol and trial plans, recruitment and retention, will be important for study optimization and sustainability of the RDCA model.

It will be important to understand what will incentivize stakeholder participation and engagement with the global clinical trials network, which will likely require a shift in standard operating procedures. If data sharing and study collaboration is encouraged, what incentives and protections will be established to promote these practices while still allowing for proprietary processes? Defining how the RDCA will support rare disease communities that are not close to therapeutic development and the steps needed to prepare the community for engagement on the development of new therapies should also be considered.

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

The components of RDCA holistically represent a significant opportunity to establish a coordinated global effort to reshape and re-envision how rare disease research and clinical trials are conducted. Certainly, an interdisciplinary leadership team must be established, and it will be essential to meaningfully include patient representation on the team from inception. Diverse

leadership will be critical to reshaping clinical trial conduct and the success of the RDCA long term.

NORD also believes that there should be some form of advisory council or board supporting the governance, and patients should have significant representation on that body as individuals or a collective entity with necessary power to exert their influence. Ideally there would be balanced disease expertise and representation across the globe but, which such a diverse group of diseases, that is a challenge and is where the other components of the RDCA can be leveraged. Similarly, the ideal structure would be to have clinical trial sites throughout the world reducing the burden for patients participating. However, there are significant challenges to establishing global clinical trial sites in the short term, an opportunity to leverage telehealth capabilities exists.

Additionally, as part of the governance framework there should be Memorandums of Understandings or agreements that spell out roles and responsibilities of all parties involved so that expectations around performance and engagement are well understood and accepted. With a project of this size and complexity it will be essential that a party's ability to complete the objectives as intended and keeps pace with the other stakeholders in the project will be fundamental aspect to the success of the clinical trial network as a whole.

The Clinical Trials network component of RDCA will also need to address cultural norms and local laws that may conflict with implementing a uniform approach to the operationalization of the network. Patients and PAG's in some parts of the world are not considered an integral part of the input and design process as they are in the US. They are considered to be more of the recipient of the process rather an integral member of the drug development process, contributing to benefit/risk analysis, the knowledge basis defining the natural progression of disease, and/or the clinical trial design.

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*)

As stated above, coordination across the three individual components of the RDCA will be critical to the success of the overall initiative. Consideration of the knowledge gained, processes established, and a reflection of opportunities to create sustainable efficiencies and linkages across components one and two should be paramount to the strategic approach to the development of component three.

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

NORD acknowledges that there may be significant challenges in establishing and sustaining a global rare disease clinical trials network, however we believe that they can all be overcome for the greater good that the RDCA promises. One such challenge is the competitive environment of drug development. Generating collaboration, engagement, information sharing, and a shift in

standard operating processes may present challenges to those with proprietary information. Another such challenge is the sheer number and diversity of known global rare diseases. As mentioned above, cultural norms and the way health care systems are structured in each region of the world participating in this is very important to take into consideration. The best laid plans established in a vacuum can fail miserably if local characteristics are not taken into consideration.

NORD encourages the designers of the network to focus on areas where work can be done efficiently to build momentum for the program. Demonstrating early success or small pilots that exemplify how the global clinical trials network will work, why it is an important contribution to the field, and the value it can bring to rare disease drug development may help the early adoption of the RDCA.

Conclusion

NORD appreciates the opportunity to comment on this important draft guidance and looks forward to working with FDA to ensure rare disease patients are able to fully benefit from these exciting and potentially life changing therapies. For questions regarding NORD or the above comments, please contact me at rsher@rarediseases.org, or 202-588-5700.

Sincerely,

A handwritten signature in black ink, appearing to read "Rachel Sher". The signature is fluid and cursive, with the first name "Rachel" and last name "Sher" clearly distinguishable.

Rachel Sher, J.D., M.P.H.
Vice President, Policy and Regulatory Affairs
NORD