



July 31, 2020

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

**Re: Docket No. FDA–2020-N-0837: Rare Disease Clinical Trial Network; Request for Information.**

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the Request for Information on the Global Rare Disease Clinical Trial Network.

BIO is the world’s largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO’s members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of diseases, and to prevent diseases in the first place.

BIO appreciates FDA’s efforts to address challenges associated with developing therapies for the thousands of rare diseases that do not yet have treatments. We further appreciate FDA efforts to seek feedback from the stakeholder community on the third component of the Rare Disease Accelerator focused on the development of a global rare disease clinical trial network. However, given the number of identified rare diseases, we have concerns and questions regarding the potential scope of a single rare disease clinical trial network. As discussed in greater detail below, it may be more appropriate to consider the development of more than one rare disease clinical trial network. It will also be important for FDA to clearly outline the scope and mission of the clinical trial network(s).

It is also important to note that rare disease drug developers still face key challenges unrelated to the availability of robust, high quality global trial networks. These challenges include limited, well-matched natural history data, lack of natural history data for less-prevalent phenotypes within a given disease, limited established or relevant endpoints and surrogate biomarkers that can be used to support drug development and regulatory decision-making, and the inability to use innovative clinical trial designs to address the logistical challenges associated with limited patient populations. To this end, in addition to the efforts focused on the global rare disease clinical trial network(s), BIO encourages the Agency to continue to support rare disease drug development through the development of disease-specific guidance, finalization of draft rare disease guidance,<sup>1</sup> and public discourse regarding the key challenges mentioned above.

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<sup>1</sup> Rare Diseases: Common Issues in Drug Development and Rare Diseases: Natural History Studies for Drug Development.



BIO encourages FDA to consider the following immediate and long-term objectives/milestones for the rare disease clinical trial network(s):

1. Establishment of a steering committee for the clinical trial network(s), including participation from patients, caregivers, patient organizations, clinicians, drug developers, and other health authorities;
2. Engagement of stakeholders through a public meeting and public comment process;
3. Analysis of existing clinical trial network(s) and development of the scope and mission for the clinical trial network(s), including potential grouping or prioritization of rare diseases to be targeted through the new network(s);
4. Development of standards for the clinical trial network(s), including common data elements, mechanisms and platforms for data/information sharing, structured institutional review board, data collection including collection of natural history data, identification of potential third parties to manage and implement the network(s); and
5. Continued engagement of stakeholders on lessons learned and opportunities for improving the clinical trial network(s).

#### **Establish a steering committee**

Initially, we encourage FDA to consider developing a steering committee to help support subsequent FDA rare disease clinical trial network(s) activities. As we elaborate below, this steering committee should have appropriate representation from key rare disease stakeholders, including disease specific experts, clinical outcome assessment experts, biostatisticians, data management experts, payers, clinicians, drug developers, and patients and patient organizations.

It is critical to understand the scope and mission of the clinical trial network(s) in order to determine what infrastructure would be required to initiate, implement and sustain the rare disease clinical trial network(s). BIO also strongly believes that global clinical trial network(s) are not possible without coordinated efforts across health authorities. Therefore, BIO requests that FDA partner with other health authorities from the onset of the initiative to truly harmonize regulatory guidance pertinent to the network(s) and to best coordinate the clinical trial network(s). BIO encourages the steering committee to consider issues such as research coordination, administrative and infrastructure considerations, as well as means to seek alignment and communication across the broad range of stakeholders.

While governance of the clinical trial network(s) is important, emphasis should also be placed on agility to respond to shifts in disease focus, regulatory changes, or use of the data for premarket marketing applications. BIO encourages FDA to ensure that staff of the rare disease clinical trial network(s) are attending/involved in scientific or first in class therapy advisory committee meetings, to understand new scientific advances and innovative therapeutics. For reference, we have outlined several models of governance that FDA may consider when establishing the governance for the rare disease clinical trial network(s).

- [Castleman Disease Collaborative Network \(CSCN\)](#)
  - The CDCN is a global initiative dedicated to accelerating research and treatment for Castleman disease (CD) to improve survival for all patients with CD.
  - CDCN works to achieve this by facilitating collaboration among the global



- research community, mobilizing resources, strategically investing in high-impact research, and supporting patients and their loved ones.
- Together, the community identifies and prioritizes high-impact research questions. It then identifies and recruits the most qualified researchers to conduct each study.
  - In parallel, patients are empowered to fundraise and providing their biospecimens and clinical data for analysis in these studies.
  - This approach democratizes research to identify the most clinically relevant and pressing questions.
- [Bone Marrow Transplant Clinical Trial Network](#)
    - The Bone Marrow Transplant Clinical Trial Network has an established model of consortium collaboration that could be referenced for best practices.
  - [Leukemia and Lymphoma Society](#)
    - The Leukemia and Lymphoma Society has convened contributors and stakeholders to work across many products in search of therapies to address acute myeloid leukemia.
  - [Amyotrophic Lateral Sclerosis \(ALS\) Association](#)
    - The ALS Association is a national non-profit organization with the mission of leading the way in global research, providing assistance for people with ALS through a nationwide network of chapters, coordinating multidisciplinary care through certified clinical care centers, and fostering government partnerships.
    - The ALS Association has recognized novel approaches that have led to significant ALS research findings.
    - The global scope aims to translate research into meaningful therapies, involves a world-renowned panel of scientific advisors, as well as having direct access to patients to participate in clinical trials.

### **Engage key stakeholders**

BIO believes that clear and transparent planning for the rare disease clinical trial network(s) will support the most successful program. To this end, BIO encourages FDA to hold a public stakeholder meeting, outlining the Agency's initial thoughts on the network(s). The public meeting will also ensure that FDA can hear from a wide range of stakeholders on the potential focus of the network(s) and ask clarifying questions.

### **Conduct global analysis to inform development of scope and mission**

Along with a public meeting, it would also be beneficial for FDA to conduct a global landscape analysis of existing rare disease clinical trial networks. Information such as the mission, objectives, process to collect and communicate information, existing links to other databases, and sources of information for each of these networks would be important for FDA to include in such an analysis. The landscape analysis should be used to identify existing sources of information, potential gaps, align with other global networks, and to ensure that a unique scope for the proposed global rare disease clinical trial network(s) can be defined.



As alluded to above, given the significant number of identified rare diseases that do not have approved treatments, as well as the heterogeneity across rare diseases it will be difficult for a single clinical trial network to address all identified rare diseases. Additionally, the needs of one rare disease community may be very different from another rare disease community. To address this challenge, BIO recommends that FDA potentially group diseases by etiology, such as genetic diseases and autoimmune diseases, by system (e.g., rare bleeding disorders, rare neurodegenerative diseases, periodic fever syndromes, liposomal storage disorders of similar etiology or symptomatology), or biomarker and/or prioritize diseases to be targeted initially within clinical trial network(s). FDA may consider soliciting public comments identifying disease areas of focus or input on potential disease grouping, establishing multiple clinical trial networks, prioritizing diseases where clinical trial networks/natural history do not yet exist, or developing a “network” of clinical trial networks.

BIO encourages FDA to prioritize developing infrastructure for rare disease clinical trial network(s) that supports the collection of high-quality data that are endorsed by the Agency for regulatory decision-making. Importantly, and as noted above, rare disease drug developers often lack natural history or comparator data describing longitudinal progression of key symptoms, age at symptom onset, age at diagnosis, gender, prognosis, biomarkers/labs reflective of disease pattern and predicting disease progression (none or stable, rapidity element, intermittent or steadily progressive) and treatment response, family history, and comorbidities, among other factors. These key elements of natural history studies are essential for rare disease drug development. To this end, we encourage FDA to focus on building robust natural history registries with data that will be rigorous enough for regulatory decision making for a wide range of rare diseases and/or adopt an approach that can work across rare diseases. In this case, repositories to share data with stakeholders would be particularly beneficial. The aforementioned landscape analysis may support leveraging existing datasets on natural history studies. Additionally, guidance from FDA outlining quality criteria for registries that can be used for collecting natural history data (similar to EMA’s Discussion Paper on Use of Patient Disease Registries for Regulatory Purposes) and/or lessons learned from existing networks such as the FDA-NORD Natural History Study Project and the outcomes from FDA Natural History Grants Program, highlighting how these data are being shaped for regulatory approval would be particularly beneficial. BIO also believes that another useful aspect of a rare disease clinical trial network(s) will be to ensure that patients and patient organizations are more aware of and able to access the network(s).

It is critical to understand the scope of the proposed network(s) to provide projections on an estimated budget for the rare disease clinical trial network(s). However, once a scope and mission for the clinical trial network(s) have been established, FDA should engage with other clinical trial networks to gain insight on the cost to establish and sustain such programs when identifying the funding needs for the rare disease clinical trial network(s). Given the large proportion of small biotech companies developing therapies for rare disease populations, BIO requests that FDA consider monetary feasibility for small biotech companies when establishing funding mechanisms for the clinical trial network(s).

### **Develop standards and sustainable infrastructure for clinical trial network(s)**



Once a steering committee has been established and FDA has engaged with various stakeholders, we encourage the Agency to identify and establish key elements for each network(s). Such elements could include, clinical trial designs, endpoints and data requirements, pre-competitive collaboration for collection of natural history data, standard of care, a clinical trial operations framework, recruitment and data management strategies, database and patient specimens, regulatory hurdles, requirements for use and access to data, and an open communication forum for evolving data and issues. These elements may need to be considered on a disease-specific basis.

**Continued engagement of stakeholders on lessons learned and opportunities for improving the clinical trial network(s).**

Throughout the development and implementation of the rare disease clinical trial network(s) BIO encourages FDA to continue to engage the stakeholder community to ensure that the network(s) continues to serve as a useful resource for rare disease drug development.

**Other Considerations:**

**Leveraging existing networks and organization structure as a model for how a global clinical trials network(s) could operate**

BIO encourages FDA to consider existing clinical trial networks when developing the mission and scope for the rare disease clinical trial network(s). As mentioned above, it may be particularly helpful for FDA to conduct a global landscape analysis of existing rare diseases clinical trial networks. It may be helpful for FDA to consider how the rare disease clinical trial network(s) will be different from other established networks, how the rare disease clinical trial network(s) may leverage the existing networks, and what gaps the rare disease clinical trial network(s) may fill. BIO also encourages FDA to consider how the rare disease clinical trial network(s) may also leverage other efforts addressed via the Rare Disease Accelerator including the development of a standard core set of clinical outcome assessments and endpoints relevant to rare conditions, on a disease specific basis.

BIO suggests FDA work with patient advocacy organizations to understand their experiences with clinical trial networks that integrate disease-specific development centers with a disease-agnostic operations center (e.g., the Friedreich's Ataxia Research Alliance [FARA] and the Multiple Myeloma Research Foundation [MMRF]). Furthermore, the Clinical Trials Transformation Initiative (CTTI) has published several recommendations on registry trials and decentralized trials, among others, that could be leveraged as the Agency considers standard procedures for the conduct of clinical trials by the network(s).

The FDA may consider referencing work underway at the National Institute of Allergy and Infectious Disease Division of Allergy, Immunology and Transplantation (DAIT) Statistical and Clinical Coordinating Center being consolidated and supported by a central contract research organization. The objective of the Center is to provide efficient coordination of the following services: protocol development, study initiation and management, statistical design and analysis, clinical site monitoring, ancillary services, data management, safety oversight, and bioinformatics in support of clinical trials related to asthma/allergic diseases, autoimmune diseases and transplantation.



FDA may consider the [Rare Disease Institute - Genetics and Metabolism](#), a model that utilizes rare disease outpatient clinics which serve as a way to connect and coordinate between different clinicians and investigators of differing specialties. This model provides a medical location for patients and families seeking the most advanced care and expertise for rare genetic conditions that remain largely unknown to the general medical community. In addition, it provides comprehensive care, including medical experts, metabolic dietitians, nurse practitioners genetic counselors, social workers, child life specialists and chaplaincy services staff, for children and their family members that have been impacted by these extremely rare genetic diseases.

### **Investigator experience needed to initiate and expand to implement a global clinical trial network(s)**

Generally, BIO believes that the expertise listed in the Federal Register notice (clinical trial research administration, clinical trial operations, working with pharmaceutical companies in the design, conduct and management of clinical trials) are all important perspectives needed to initiate and expand global clinical trial networks. BIO also encourages FDA to consider inclusion of clinical pharmacologists, geneticists, pre-clinical scientists, clinical experts, contract research organizations (CROs) data scientists, epidemiologists, clinical project managers, and statisticians and biometric experts. FDA should also consider experts with experience with biomarkers, surrogate endpoints, patient reported outcomes and pediatric populations. FDA should ensure that those involved in initiating and implementing the global clinical trial network(s) receive appropriate Good Clinical Practices training. Consistent with the Agency's patient focused drug development initiatives, BIO also encourages FDA to place an emphasis on input from patients and patient advocacy organizations throughout the development and management of the rare disease clinical trial network(s).

### **Opportunities to address barriers and challenges**

We appreciate that FDA is committed to enhancing the ability to conduct clinical trials in rare disease. However, there are significant challenges that should be considered prior to initiating a global rare disease clinical trial network(s). We have outlined below several of these challenges along with potential mechanisms for addressing such challenges.

#### **Clinical trial network infrastructure:**

- Challenge: Lack of unifying and focused scope and mission
  - Possible solutions:
    - FDA will need to balance potential competing stakeholder priorities and priorities for different rare diseases
    - FDA should hold a public meeting and solicit written comments from stakeholders on the scope and mission of the clinical trial network(s)
    - FDA may consider establishing a steering committee with representation from key stakeholders to address this challenge
    - FDA may consider streamlining the process for gathering stakeholder input via a steering committee with clear expectations defined upfront
- Challenge: A lack of funding for identified scope and mission
  - Possible solutions:
    - FDA should first form a steering committee to help establish the scope



and mission, once the scope and mission had been determined it will be much easier to understand what level of funding is needed and how funding may be obtained

- Challenge: Heterogeneity and number of identified rare diseases
  - Possible solutions:
    - When establishing the scope and mission, FDA should consider whether rare diseases can potentially be grouped by etiology, such as genetic diseases and autoimmune diseases, by system (e.g., rare bleeding disorders, rare neurodegenerative diseases, periodic fever syndromes, liposomal storage disorders of similar etiology or symptomology), or biomarker and/or prioritize diseases to be targeted initially within clinical trial network(s)
- Challenge: Lack of harmonization across FDA and EMA and other health authorities regarding rare disease regulatory policy
  - Possible solutions:
    - FDA should consider engaging with other health authorities early in the process of developing the clinical trial network(s)

#### Clinical Trial Network Design:

- Challenge: Lack of consistency of clinical trial operations across clinical sites
  - Possible solutions:
    - Develop a framework, resources, and expectations for clinical trial operations
    - Consider establishing best practices or guidelines for clinical operations
    - Consider providing template protocol documents
- Challenge: Difficulty recruiting patient to participate in the clinical trial network(s)
  - Possible solutions:
    - Early consideration of how to reach and enroll diverse patients
    - Early consideration of how to get the patient to the drug or the drug to patient
    - Early consideration of how to collect and manage data that maximizes the potential to enroll patients broadly and not necessarily at limited trial sites
    - Early consideration of conducting educational outreach to increase clinical trial enrollment, access, and participation by patients and physicians at qualified clinical trial sites
    - Early consideration for performing clinical development work and how best to provide clinical trial access in developing countries
    - FDA should also consider diagnostic efforts that may assist in enrollment for the network(s)

#### Clinical trial design:

- Challenge: Lack of robust and flexible trial designs
  - Possible solutions:



- Evaluate whether there is a way to combine certain diseases into a single trial design if disease pathology, natural history, biomarkers, or drug mechanism of action overlaps across diseases or subsets within a broader disease spectrum (e.g., MSI-H tumors in oncology, Sanfilippo syndrome type III A-B-C-D, severe and attenuated phenotypes across the same disease spectrum, among others)
- Consider that single arm designs may be needed for the network(s). For rare diseases with no treatment options and rapid disease progression, randomized, parallel trial designs with a concurrent control group may not be feasible or ethical. Non-concurrent, appropriately matched, historical control groups should be the basis for the clinical development of new therapies for these disorders. Every effort should be made to foster a pre-competitive collaboration between key stake holders to gather the most appropriate data sets for regulatory purposes
- Sample size should be considered in the context of demonstrating safety or efficacy
- FDA may consider providing recommendations on criteria of a robust historical or synthetic comparison arm

Data Quality/Access:

- Challenge: Data collected in the clinical trial network(s) may not meet standards for regulatory decision making
  - Possible solutions:
    - Consider defining types and quality of data considered essential and complete for an approval path
    - Consider developing guidelines for the type of data to be collected, cleanliness of data, and adequacy of data for potential drug approval
    - Consider developing guidance on how to best collect data in the context of registries, similar to the EMA Discussion Paper on Use of Patient Disease Registries for Regulatory Purposes
- Challenge: Lack of stakeholder timely access to clinical trial network(s) data
  - Potential solutions:
    - Ensure access to data by all partners in the trial process to efficiently move the drug forward for patients
    - Early on establish a governance for database ownership and access

BIO appreciates this opportunity to submit comments regarding FDA's Request for Information on Rare Disease Clinical Trial Network(s). We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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Senior Director, Science and Regulatory Affairs

Biotechnology Innovation Organization