July 31, 2020

Stephen Hahn, MD
Commissioner Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2020-N-0837, Rare Disease Clinical Trial Networks; Request for Information and Comments

Filed electronically at regulations.gov

Dear Commissioner Hahn:

On behalf of the Cystic Fibrosis Foundation and the Cystic Fibrosis Foundation Therapeutics Development Network (TDN), we write to provide comments in response to Food and Drug Administration's (FDA) request for information on rare disease clinical trial networks. We appreciate this opportunity to share our thoughts on establishing and operating a successful rare disease clinical trial network. Our comments below reflect our significant experience and observations in operating a national clinical trial network for the cystic fibrosis community. We hope the agency will continue to engage patient organizations beyond this comment period as work on the Rare Disease Cures Accelerator initiative progresses.

Background on Cystic Fibrosis and the CF Foundation

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis – a rare, life-threatening genetic disease that affects more than 30,000 people in the United States. The CF Foundation has been engaged in virtually every element of the research and development process, from preclinical discovery to identification of new therapeutics to conducting clinical trials as well as post-market surveillance and quality improvement studies.

The CF Foundation has significant experience with the process of rare disease drug research and development. When the Foundation was formed in 1955, no CF-specific drugs existed. However, by raising and directing funds needed to fuel cystic fibrosis drug development programs, the CF Foundation has encouraged pharmaceutical companies to invest in rare disease research. Additionally, with the Foundation's Therapeutics Development Network (TDN) – the largest cystic fibrosis clinical trials network in the world – we have been able to spur clinical trial designs that work for the CF community and address barriers to clinical trial participation. Since 1998, the TDN has conducted more than 130 clinical studies for cystic fibrosis in a wide range of therapeutic areas, including restoring CFTR function, mucociliary clearance, anti-inflammatory, anti-infective, and nutrition-gastrointestinal. Today, there are 14 therapeutic products available in the United States to treat people with CF, four of which treat the underlying cause of the disease.

Our comments below address key features we believe are helpful for creating an environment where a rare disease clinical trial network can thrive. We would be pleased to share more on our considerable experience with clinical trial networks with the FDA as the agency continues its work to support rare disease therapeutic development through the Rare Disease Cures Accelerator initiative.

Building Trust with Patients is Key

The success we have seen with cystic fibrosis clinical trials is due in part to having research centers co-located at specialty care centers. There are more than 130 specialized CF care centers across the country. CF care centers are accredited by the CF Foundation and provide multidisciplinary, specialized care in accordance with evidence-based guidelines.

Importantly, this model allows for patients to build strong relationships with their care teams, and those relationships create opportunities to build clinical trial participation. Patients want to hear about clinical trials from their care team who they know and trust. Because of this dynamic and the fact that TDN investigators and research staff are located at the same site as CF care teams, we are able to better promote and engage the community in cystic fibrosis clinical research to ultimately speed the delivery of new and better therapies to people with CF.

Patient organizations can also serve a critical role in building trust and disseminating information to patients. Patient organizations often serve as a convener for patients in the community, collect and disseminate disease and care information to community members as well as the broader public, and express community needs with one voice. Fostering a culture that encourages patients to participate in clinical trials is important to ensuring the success of a clinical trials network that serves small populations, and patient organizations or other trusted sources of information have the power to facilitate this process.

The CF Foundation has regular communication with our patient community on the value of participation in clinical trial, and this has helped build a community that is motivated to participate in trials. For many people with CF, clinical trials represent a crucial opportunity to access potentially life-changing treatments and prevent further health decline. Of note, many individuals with cystic fibrosis also recognize that trials present a valued opportunity for individuals to contribute to advances that can benefit the broader disease community. Thanks to having strong community buy-in on clinical trials, we have been able to successfully carry out a wide range of studies across the network despite having a relatively small patient population to draw from.

Building trust in clinical trials may be more challenging to do in a disease agnostic clinical trials network setting in the absence of a trusted source of information that speaks to the needs of each given patient population. Bringing organizations that represent patient communities into the development and operations of a rare disease clinical trial network will be important for the success of that network. Where no such organization exists, FDA should consider other ways to facilitate reliable and regular communication that speaks to unique patient population challenges and needs.

Retaining Clinical Trial Expertise is Important

Clinical trial sites need a financial model that helps retain expertise and trained support staff. This is particularly valuable for rare disease clinical trials, where having the appropriate expertise is necessary for understanding the nuances of the disease as well as the unique challenges experienced by the patient community.

Our clinical trial network benefits immensely from cultivating and retaining the right expertise to carry out studies at individual clinical trial sites across the U.S. Because we are able to retain trained research staff from one study to another at these sites, the staff that support CF clinical trials have gained important knowledge on how best to carry out those studies and serve the patient community. Furthermore, CF clinical research staff are able to build relationships with community members who receive care regularly at that site. Offering programs to recruit and support research staff, such as programs modeled after the CF Clinical Research Coordinator Mentoring Program, could be established to help cultivate and retain the expertise needed to make rare disease trials successful.

The role of experienced translational research staff and trial design experts cannot be overstated in ensuring the success of clinical trials supported by a network. For rare disease clinical trials, more traditional clinical trial designs may not be feasible or ethical. A clinical trial program simply connecting patients with trial sponsors is not enough to be successful. Quality trials need to be cultivated and prioritized for a rare disease clinical trial network to be successful in producing therapies that benefit the patient community.

Rare disease communities often face unique challenges such as small patient populations, poor disease characterization, and wide range of disease presentation that make it more difficult to carry out traditional clinical trials. It is important to have the right expertise to ensure clinical trials supported by the network work for the unique challenges of rare disease patient communities. The TDN retains valuable expertise in clinical trial designs that work for the CF community. With this expertise, we are able to provide collaborating investigators and sponsors access to resources that will help them ensure efficient study design, optimized clinical trial execution, and the highest-quality data for their CF clinical trials.

Adequate Basic Science Knowledge and a Robust Drug Development Pipeline are Necessary for Success

Facilitating robust and sustainable funding for rare disease research will be crucial for advancing rare disease therapies. Basic science on a given rare disease must be advanced enough to support therapeutic development. Not only is it vital to have a thorough understanding of the disease for finding therapeutic targets, we also must have reliable outcome measures established for a given disease to understand whether a potential therapy ultimately benefits the patient. If the science on a given disease is not mature, it will be difficult to spur meaningful therapeutic development.

Additionally, steady funding and support for products in development throughout the pipeline is key for attracting researchers and companies to a rare disease space. Nearly every CF drug available today was made possible because of the CF Foundation's support and its ongoing work with researchers. The reliable support the Foundation provides encourages new companies and researchers to engage in CF research while helping to maintain those who already work in this space. It’s important that rare disease

clinical trial networks facilitate trials for conditions where the science is advanced enough to support therapeutic development and sustainable funding is available to attract and retain drug developers in a given disease space.

The lack of established natural history for many rare diseases poses a significant barrier to basic science, and clinical research and patient registries can help to fill this knowledge gap. Registries are an invaluable source of patient population data and are essential for speeding the overall process of rare disease drug development. A patient registry can also provide valuable information for planning clinical trials, including informing site selection based on where target populations are located. Since 1986, the CF Foundation has maintained a patient registry that includes vital clinical care data about those living with CF. The Foundation registry is a unique and rich source of real-word data that has been leveraged for a number of purposes including developing CF care guidelines, optimizing standards of care in an age of disease-modifying CF drugs, and supporting observational studies. Support for rare disease patient registries will be important for advancing understanding of a given disease and informing clinical trials that must overcome challenges related to small patient populations.

A Global Rare Disease Network May Not Be Optimal or Feasible

Clinical trials for both adults and children need to draw on global patient populations with increasing frequency. This is especially true for rare genetic disease populations like CF, where trials may need to access populations of patients from around the world in order to overcome small patient pools in any given country. As a result, it is imperative that clinical trial designs, endpoints, and the timing of studies are coordinated between global regulatory agencies such as the European Medicines Agency (EMA) and the FDA. However, currently a lack of harmonization between regulators in different countries or regions poses a significant barrier to global rare disease clinical trials.

Pediatric clinical trials remain important for improving outcomes for patients living with CF; however, pediatric studies in particular pose a number of challenges when coordinating global clinical trials. For example, the EMA currently requires a pediatric investigation plan (PIP) at the end of phase 1 of development, whereas the FDA requires submission of an initial pediatric studies plan (iPSP) much later in development. This discrepancy in timing can create additional challenges for drug developers, and better coordination between regulatory agencies on the timing of pediatric plans is needed to avoid unnecessary delays during the pediatric drug development process.

CFF is engaging globally on clinical trial studies by working with our CF clinical trial network peers in other countries.[1] This informal confederacy of networks allows each group to operate separately and regionally in a way that allows for more agility and responsiveness to regional regulatory requirements and standards, while still allowing for global collaboration on clinical trials. For example, as part of our efforts, we have worked with CF clinical trial networks in Europe and Canada to harmonize scientific protocol review processes for drug developers looking to develop a product across these regions. However, each regional network is still able to respond to the unique local environment and maintain regional expertise on regulatory expectations and patient needs and preferences. Encouraging collaboration between different regional networks may be more beneficial for spurring successful

[1] https://www.cysticfibrosisjournal.com/article/S1569-1993(20)30161-2/abstract

therapeutic development than operating a single global clinical trial network that is less flexible and responsive to regional regulator expectations and patient needs.

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Once again, we thank the FDA for this opportunity to share our experience with cultivating and operating a rare disease clinical trial network. There are important opportunities for collaboration and discussion regarding the agency's work to support rare disease drug development, and we stand ready to work alongside the FDA in the future in this endeavor.

Sincerely,

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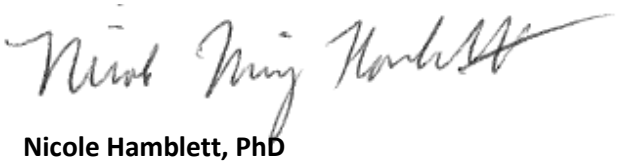

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