BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL

MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

July 20, 2020

Submitted electronically at www.regulations.gov

The Honorable Stephen Hahn, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20990

RE: Docket No. FDA-2020-N-0837, Rare Disease Clinical Trial Networks; Request for information and comments (and containing information relevant to Docket No. FDA-2019-N-5464).

Dear Commissioner Hahn:

The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (MRCT Center) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s request for information and comments on the potential development of a rare disease clinical trial network, with the specific intention to establish a Rare Disease Cures Accelerator. The request for information and comments here relate specifically to improving the design, conduct and completion of rare disease clinical trials, and we offer high level comments, not detailed responses to each question. In making these comments, we note that the MRCT Center is currently working on an initiative to improve the ethics, conduct, and oversight of pediatric clinical trials, and several FDA members have participated in some of those conversations. We offer the comments here independent of their participation; we have not discussed these comments with anyone at FDA. The responsibility for the content of this document rests with the leadership of the MRCT Center and not with the institutions affiliated with the authors.[1]

The MRCT Center is a regulatory policy center that addresses the ethics, conduct, oversight, and regulatory environment of international, multi-site clinical trials. Founded in 2009, it functions as an independent convener to engage diverse stakeholders from industry, academia, patients and patient advocacy groups, non-profit organizations, and global regulatory agencies. The MRCT Center focuses on pre-competitive issues, to identify challenges and to deliver ethical, actionable, and practical solutions for the global clinical trial enterprise. In addition, the Center is involved in several ex-U.S., in-country engagements and has a long-standing commitment to training global regulators, investigators, and others. As mentioned, over the last year, the MRCT Center convened a working group to address the challenge of global clinical research in children, charged with aligning ethical, practical, and regulatory approaches.

[1] Brigham and Women's Hospital, Harvard Medical School, and Harvard University.

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It is important to say at the outset that the MRCT Center **fully supports the mission and direction of the Rare Disease Cures Accelerator.** We wish to draw attention to the needs of pediatric research, and we underscore that pediatric diseases are generally rare and ultrarare diseases. We recommend that **pediatric diseases be a central focus** of the Rare Disease Cures Accelerator and that the Accelerator be optimized to facilitate the design and conduct of pediatric clinical trials.

The **challenges of pediatric trials** reflect many of the same challenges of rare disease trials: small numbers of patients, lack of standard data collection methods or consistent outcome measures, few trials either initiated or completed, and hesitancy to share data out of concern for privacy and confidentiality. We believe that one area on which to concentrate is the further development of **novel and innovative approaches to study design**. Master, platform, and adaptive study designs appear to be helpful in speeding reliable evidence generation, and further development and implementation of these approaches are needed. There are already several very helpful examples (e.g. Spinal muscular atrophy, Duchenne muscular dystrophy), but they are few in number. Additional approaches should be evaluated, including the possibility of introducing flexibilities in design and conduct (e.g., decentralized trials, use of mobile technologies) that would not interfere with data integrity or the robustness of the evidence base.

In addition, given the paucity of patients in rare and ultrarare diseases, we recommend that work on **approaches to statistical analyses** be undertaken, to consider what flexibilities or alternative methods might be entertained. Bayesian approaches appear to be helpful particularly in the setting of rare diseases.

The **establishment of clinical trial networks** should be further considered. We note that there are already robust networks dedicated to one or other therapeutic areas that should be engaged in the Rare Disease Cures Accelerator, and that a "network of networks" may be one operational plan to consider. We believe that the day-to-day operations of any clinical trial network would need to be at arm's length from the regulatory agency (given that the FDA will inspect and have oversight), but that involvement of the Rare Disease Cures Accelerator in a private-public partnership might allow the agency to provide a mechanism to support the infrastructure needed, disease-agnostic platforms, and dissemination of lessons learned. The development of future therapeutics depends upon collaboration.

It does appear that the current request for information focuses on the optimization of allocating patients who have already been identified as having a rare/ultra-rare disease to one or other trials, and questions that then arise in clinical trial design and conduct. We wish to highlight attention to **screening for rare conditions**, including screening for less severe subtypes of a condition or a subtype of uncertain severity, and whether and how to expand the use of genome sequencing in screening endeavors. More generally, the Rare Disease Cures Accelerator should consider **issues of identification and eligibility**. There are **ethical considerations** such as identifiability,

privacy, and potential discrimination to be addressed by the Rare Disease Cures Accelerator as well, issues that are particularly salient for newborns and children.

Like trials for rare diseases, there is a growing appreciation of the **need for international trials** for sufficient enrollment. Currently many pediatric clinical trials that test investigational products are international, and this should be anticipated and encouraged by the Rare Disease Cures Accelerator.

Any clinical trials effort that is intended to be a **global network** should include regulators from well-resourced regulatory agencies as well as those from emerging economies. Alignment and harmonization, or at a minimum convergence, of regulatory expectations, processes, required submissions, timelines, common data standards, analyses, and evaluation will be necessary to optimize the efficiency of clinical trials, essential for evaluation of all products, including diagnostics, drugs, biologics, vaccines, and devices. We find that different regulatory agencies request or require different study designs and outcomes for trials that render international cooperative, multi-site trials unnecessarily difficult or impossible to conduct. The FDA should work directly with other health regulatory authorities to adopt common approaches. Agreement, in advance, on study design, essential eligibility criteria, outcome measures, and statistical approaches will be important. Clinical research should feature outcome measures that are relevant and important to children and their families. We believe that platform trials, designed through global cooperation of regulatory agencies, industry, and others will minimize the numbers of participants required while optimizing robust scientific evidence and efficiency, and are a necessary focus of consideration.

From the RFI, it is difficult to know what is meant by "global," and whether the FDA envisions an actual international clinical trials network of sites, and if so, how that will be organized and supported. Of course, there are robust, established networks for rare diseases and pediatric clinical trials outside the USA (e.g. conect4children [c4c] in the EU, funded by the IMI). The proposed network should partner with these initiatives if a clinical trial network is envisioned. If the Rare Disease Cures Accelerator is planned as a network of networks and/or international organizational initiative, then financial and other resource commitments outside of the US should be considered, as should strategic partnerships with others.

While the clinical trial design, approach, and analysis and product evaluation may be cooperative, it is assumed that each regulatory agency, responsible for the health and protection of its own population, will render independent decisions as to whether a product will be approved and, if approved, whether placed on formulary. We believe that clinical trials should only be conducted in countries, in locations, and on populations that will have access to the product if approved. **International members** should be included from the outset of the Rare Disease Cures Accelerator.

We believe that success of the Rare Disease Cures Accelerator will demand a **governance structure** that includes a leader or leaders of the network, possibly by therapeutic area, with the vision, respect, and gravitas to engage the necessary stakeholders to effect change. Further,

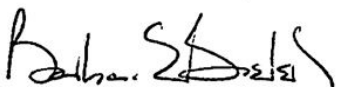
representatives from regulatory agencies, biopharmaceutical industry, academia, patients and patient advocates, clinical research organizations, and clinicians, among others, should be included in discussions.

Thank you again for the opportunity to comment on this important initiative, a plan that will impact all patients afflicted with rare and ultrarare diseases and their loved ones. This initiative, envisioned as a global cooperative, will advance the understanding of pathobiology, diagnosis, treatment, and prevention of pediatric diseases. We are encouraged by the proactive efforts of the FDA to address these salient issues.

We are available to discuss our comments with you if that would be helpful and would be happy to work with you on any of the aforementioned items. Please feel free to contact the MRCT Center or Barbara Bierer, MD, bbierer@bwh.harvard.edu; (617) 827-7413 (cell).

We look forward to working with you and would be happy to assist if we are able to be helpful.

Respectfully submitted,



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on behalf of
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