AMERICAN EPILEPSY SOCIETY

Lowell J. Schiller,
Principal Associate Commissioner for Policy.
Food and Drug Administration

Re. Docket No. FDA-2020-N-0837
Request for Information/Comments (RFI) on
Rare Disease Clinical Trial Networks

July 29, 2020

Dear Mr. Schiller,

Please find attached comments from the American Epilepsy Society on the above referenced RFI. AES is the professional society of 4500 healthcare professionals and scientists committed to epilepsy research and the care of individuals afflicted with epilepsy.

AES appreciates the opportunity to comment and publicly endorse the concept of an FDA-sponsored set of networks for rare disease clinical trials, a program that would be extremely beneficial for the rare disease community.

Sincerely,

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American Epilepsy Society (AES)
Written comments to
Lowell J. Schiller,
Principal Associate Commissioner for Policy.
Food and Drug Administration

Re. Docket No. FDA-2020-N-0837
Request for Information/Comments (RFI) on
Rare Disease Clinical Trial Networks

AES Written Comments were reviewed and approved by the AES Research & Training Council and the AES Executive Committee in July 2020. Comments were authored by the AES FDA RFI Workgroup: Renée Shellhaas MD MS (Chair), Zachary Grinspan MD MS, Avani Modi PhD, and Eric Marsh MD PhD.

Submitted on July 31, 2020

The American Epilepsy Society (AES) is honored to submit its suggestions to the FDA regarding Rare Disease Clinical Trial Networks. Our comments reflect the integrated viewpoints of our Society, whose membership of 4500 epilepsy professionals includes scientists and clinical care providers for children and adults with epilepsy, seizures, and related disorders.

AES is pleased to endorse the concept of an FDA-sponsored set of networks for rare disease clinical trials - this program that would be extremely beneficial for the rare disease community. The epilepsy field is on the verge of potentially dramatic advancements that stem from the discovery of genetic etiologies and the imminent possibility of precision therapies. As many of the epilepsies arise from rare or ultra-rare etiologies, ***there is an urgent need for a rare disease clinical trials network for the rare epilepsies. This network would provide the necessary infrastructure and opportunity to transform these advances into meaningful improvements in patient care***.

There are hundreds of genes associated with epilepsy – many of these genes cause syndromes in which the primary symptom is epilepsy, while others underlie rare diseases for which seizures are a component but are not the most prominent feature. These rare diseases can affect people from the first year of life into adulthood. *Children and adults with rare epilepsies are medically fragile, with serious and complicated chronic conditions for which there are currently no cures and, in most cases, no disease-modifying treatments.*

Uncontrolled seizures are associated with long-term neurodevelopmental disabilities. Seizure-freedom is the primary goal for treatment of the rare epilepsies and must be the first priority. However, **as with other rare diseases, a comprehensive approach to clinical management and to practice-changing trial design for the rare epilepsies must incorporate key additional outcomes**, including developmental trajectories of neurocognitive, behavioral and

motor domains, sleep regulation, and mortality. With this background, we provide the following suggestions for a network using the framework of the questions provided in the FDA RFI:

Question 1: What are the immediate and long-term objectives of a global clinical trials network?

Immediate objectives of the Global Clinical Trials Networks should include infrastructure and governance development, as discussed in our responses to questions 2 and 4, in order to facilitate the long-term vision and potential of this transformative program. Governance should include high level representation for rare diseases that are associated with seizures. Seizures are a debilitating and unpredictable symptom of neurological disease and an important endpoint for clinical trial design. However, there are important subtleties that require expertise. For example, there are numerous epilepsy syndromes, many several different kinds of seizures, and multiple approaches to track seizures.

In the long-term, our hope for the new FDA rare disease clinical trials networks is that they will enable efficient, equitable access to cutting-edge clinical trial opportunities for all people with rare epilepsies. Ultimately, we envision support for a global consortium of epilepsy clinical trial research centers with a culture that values efficient, systematic advancement of the evidence base for treatment of the rare epilepsies. It will be important for the clinical trials networks to have available grant mechanisms to support a range of trials. The supported trials should encompass a variety of study designs and address a spectrum of goals (e.g., industry-sponsored trials of new drugs, investigator-initiated trials, comparative effectiveness trials, drug repurposing studies, and behavioral intervention trials).

Question 2: How could a global clinical trials network be organizationally structured?

We envision a tiered structure of clinical trial networks, with an overlying Rare Disease Network that provides a robust, yet efficient, administrative structure to handle interactions between the FDA (and European and Global governmental entities), industry, and care providers. *Within this central network, there must be support for central cores* that provide necessary guidance and resources for successful trials. Examples of critical cores include: trial design, biostatistics/data coordinating center, regulatory oversight, clinical coordinating center, genetics, EEG, imaging, outcomes assessment, data safety and monitoring committee, communication and dissemination, and study team training. Also essential for rare disease trials are a cutting-edge bioinformatics team and a robust neurodevelopmental, behavioral, and cognitive outcomes core. Pediatric epilepsy representation in these cores is critical because of the complexities of using seizures as a key outcome.

We advocate for specific investment in clinical informatics infrastructure to specifically support three critical aspects of the networks. "Clinical informatics" in this context refers to the development and implementation of electronic health record (EHR) technology for rare diseases. First, high quality EHR data from multiple centers would allow rapid estimates of the core epidemiology for rare diseases (i.e. incidence and prevalence), which would allow investigators to develop study designs appropriate for the number of potentially available subjects. Second, high quality EHR data could support efficient natural history studies - i.e., rapid review of the charts of individuals with specific rare diseases would allow for an estimate of the contemporary natural history of the disease. Third, regular queries of EHR data could help identify individuals for recruitment into trials, and automated reminders to participants' clinical teams can help with retention.

Many rare diseases, including the rare epilepsies, have a significant impact on neurodevelopment. The complexity of patients who are affected by the rare epilepsies was clearly demonstrated by a web-based survey of 795 patients (from 30 distinct syndromes) identified through the Rare Epilepsy Network. Greater than 50% of respondents indicated that their child had 5 or more different types of comorbidities. The most frequent comorbidities reported included learning, sleep, mental health and oral challenges. Thus, in rare epilepsies, relying on a single endpoint related to seizure frequency is not an adequate measure of impact. ***It will be essential for a new trials network to engage a multi-stakeholder panel to develop a core set of neurodevelopmental outcome measurement standards.*** The currently available standards (e.g. NIH Toolkit) do not contain relevant measures for very young children or for individuals of any age with significant cognitive and motor impairment. This is a critical knowledge gap that must be addressed in order to support rigorous clinical trials

Question 3: What kind of investigator experience is needed?

As we outlined in question two, examples of critical cores include: trial design, biostatistics/data coordinating center, regulatory oversight, clinical coordinating center, genetics, EEG, imaging, outcomes assessment, data safety and monitoring committee, communication and dissemination, and study team training in addition to expertise in pediatric epilepsy. Also essential for rare disease trials are a cutting-edge bioinformatics team and a robust neurodevelopmental outcomes core. Pediatric epilepsy representation in these cores is critical because of the complexities of using seizures as a key outcome.

In addition, for any individual trial, disease-specific and content-specific expertise is needed.

Question 4: What are successful models of governance?

An ideal governance structure for the FDA Rare Disease Clinical Trials Networks will be centered on a multistakeholder leadership team that oversees a group of key central cores that individual networks will leverage for their specific needs. The

leadership core should include physicians, other health care providers (e.g., nurse practitioners, psychologists, social workers), patient advocates, pharmacologists, as well as experts in clinical informatics, clinical trials, genetics, and regulatory aspects of drug development. The leadership team should have ready access to an identified pool of disease specific experts; **we strongly urge that experts in clinical epilepsy and neurodevelopment be included in that pool.**

Question 5: What are potential opportunities to leverage and/or complement other existing networks?

The epilepsy community has a track record of successful collaborative research networks that can provide the key experience required to bring contemporary scientific discovery to clinical trials. Thus, in addition to well-known networks whose infrastructure and approaches must be considered (e.g. the Children's Oncology Group, NeuroNEXT, and the Cystic Fibrosis Foundation Therapeutic Development Network), we highlight the following epilepsy-specific groups that can provide unique perspective:

1. The Epilepsy Study Consortium (TESC) is an independent group of investigators based in academic centers that interfaces with industry to advance new therapies. TESC has been highly successful in building partnerships between academics, industry, and regulatory agencies and optimizing clinical trial design in order to facilitate and expedite development of new treatments.
2. The Rare Epilepsy Network (REN) brings together stakeholders to address the research needs of rare epilepsy patients and their caregivers. Originally funded by PCORI, REN has grown to include 45+ patient advocacy organizations that each represent a rare epilepsy. Using knowledge and infrastructure from these groups can ensure that the FDA rare disease clinical trial networks get started quickly and efficiently.
3. The Pediatric Epilepsy Learning Healthcare System (PELHS) is a consortium of more than 20 US pediatric epilepsy centers. 13 of these have submitted EHR extracts that include information on more than 100,000 children with epilepsy to support clinical research and quality improvement. PELHS developed an EHR form that includes specific fields to identify children with rare epilepsies. This network may be valuable to the FDA for (a) direct work with children with rare epilepsies and (b) development of a deeper understanding of how clinical data research networks and LHSs function, including successes and failures.
4. The Epilepsy Learning Healthcare System (ELHS) is another epilepsy learning healthcare system project, focused on adults and children with epilepsy, whose mission is to implement a system of co-production to improve outcomes for people with epilepsy and their families. ELHS has been particularly successful at engaging patients and families in establishing their network. ELHS is also the only neurology focused network that works with the Anderson Center in Cincinnati. The Anderson Center uses a network-of-

networks approach to their work in quality improvement and may be a valuable source of advice to the FDA.

5. The Pediatric Epilepsy Research Consortium (PERC) is a network of 55 academic pediatric epilepsy programs with the goal of providing network and infrastructure to improve the care of children with epilepsy through collaborative practice-changing research. PERC investigators have participated or lead trials for rare epilepsies, such as Dravet Syndrome and the Lennox Gastaut Syndrome, including trials of cannabidiol and fenfluramine. They are likely to valuable to the FDA as a source of expertise for conducting such trials
6. The National Institute of Neurologic Disorders and Stroke (NINDS) supports a variety of infrastructure resources that could be leveraged for use with a rare disease clinical network. These resources include the NeuroBioBank that serves as a national resource for investigators utilizing human post-mortem brain tissue and related biospecimens for their research to understand conditions of the nervous system; the NINDS Human Genetics Resource Center that stores and distribute genetic samples, lymphoblastoid cell lines, and clinical data to aid in the discovery of genes involved in neurological disorders; and the NINDS Human Biosample Repository (BioSEND) that houses and distributes biosample collections from a number of natural history studies and clinical trials.

Question 6: What infrastructure is required to startup, implement, and sustain a global clinical trials network.

Other successful research networks, such as NeuroNEXT, Cystic Fibrosis Foundation Therapeutic Development Network, and Children's Oncology Group have financial support from various sources (e.g., NIH, Industry, Donors) to ensure support for trials throughout the pipeline. These funds are used to support infrastructure (see for example the cores outlined in our response to Question 2 & 3), as well as a dedicated study site team that includes site investigators and research coordinators. This is critical for consistency and for long-term development of expertise, efficient implementation of new protocols, and effective longitudinal follow-up.

Question 7: What level of funding would be needed to establish and sustain a network?

While a detailed recommendation regarding the required level of funding is beyond the scope of our response, we highlight the following consideration: Other successful research networks, such as NeuroNEXT, Cystic Fibrosis Foundation Therapeutic Development Network, and Children's Oncology Group have financial support from various sources (e.g., NIH, Industry, Donors) to ensure support for trials throughout the pipeline. These funds are used to support infrastructure, as well as a dedicated study site team that includes site investigators and research coordinators. This is critical for consistency and for long-term development of

expertise, efficient implementation of new protocols, and effective longitudinal follow-up.

Question 8: What are the key milestones and associated timelines?

We would be happy to comment on this question once the overall structure and scope of the network is established.

Question 9: What are potential challenges or barriers to starting up, implementing, and sustaining a global rare disease clinical trials network?

While we enthusiastically support the development of a rare disease clinical trial network, we can anticipate barriers to the effective functioning of such a network.

1. As epilepsy professionals, we highlight that ensuring equitable academic credit for individuals who participate in the network - whether as leaders or contributors - will be essential to obtain buy-in from institutions and providers. Furthermore, appropriate reimbursement of investigator time is needed as individuals may volunteer to get a network off the ground, but continued success requires support at all levels (see also our reply to question 7).
2. Equity in resource allocation across the rare diseases is a major challenge. While some rare diseases have strong, well-resourced, and highly organized patient advocacy groups, others do not. In some cases, scientific progress and equitable access to resources for research are hindered by a lack of strong sponsorship from a charismatic advocacy organization. We urge the FDA to consider ways to balance the scientific promise and potential impact of new treatments with optimal access to people across the sociodemographic spectrum.

To summarize, we strongly support the FDA proposal to generate rare disease clinical trial networks. The rare epilepsies are perfectly suited for such networks, as the existing treatments are largely inadequate, but the trajectory of scientific advances demonstrates the promise of novel treatment strategies. A trial network focused on the rare epilepsies would generate knowledge applicable to a myriad of other disease groups and would benefit from networking with such groups. This is a visionary and potentially transformative strategy that could result in tremendous impact for people affected by rare disease. We would be happy to comment further should the FDA have additional specific questions about this response.