2024 Research Roundtable for Epilepsy (RRE)

Drug Development to Address Non-Seizure Outcomes Associated with Epilepsy
April 25th and 26th, 2024

The Research Roundtable for Epilepsy (RRE) is an initiative of the Epilepsy Foundation to facilitate the development and implementation of new treatments and diagnostic tools for people with epilepsy, by collectively addressing roadblocks to research and development. Each roundtable focuses on a single critical issue and allows an in-depth discussion in a pre-competitive space.

The 2024 RRE was held April 25th and 26th in Washington DC, convening researchers, caregivers of people living with epilepsy, 30 companies with therapies in development for epilepsy as well as regulators from the FDA and others met for discussions. A summary of the discussion and conclusions are included below.

Electronic diaries

- The entry look-back period should have a rationale for a fixed duration.
- E-diaries should reflect the information about how information was obtained. You should prespecify and document a plan, and respect the burden to patients.
- The entry in an e-diary can serve as the source document.
- When adequately justified, caregivers or observers can be the reporter with explanation. if it changes, that also requires justification.
- Paper diaries are acceptable.
- eDiary criteria should be determined prospectively and entered in the protocol.
- Review eCOA consortium resources (white paper on best practices to come), PFDD and DHT for e-COAs but interviews and focus groups are acceptable for usability but not for selecting outcome measurements.

Non-seizure outcomes for DEE

- Seek input from FDA early in development, especially before developing a novel or complicated primary outcome intended for a critical clinical trial
- Pay attention to Context of Use
- Multicomponent Analysis, Most Bothersome Endpoint, and Adequate Relief Endpoints have been used in efficacy analyses supporting FDA-approved drugs.

- Multidomain Responder Index and Goal Attainment Scaling may have complicated methodological and analytical issues that make them complicated as primary outcome measures but may be considered as exploratory outcomes. These exploratory outcomes might be able to provide supportive evidence.
- Qualitative exit interviews are an important and useful mechanism to capture information on meaningful change, especially in the use of outcomes with more limited prior development.
- Although designation of a primary outcome assessment is important, careful selection of complementary secondary and exploratory endpoints is encouraged and plans should be included for a rigorous evaluation of all data, usually with pre-specified hierarchical evaluation.
- Trial length is likely to be longer than for a traditional seizure study, for a non-seizure outcome study.
- Important and meaningful non-seizure comorbidities that represents important aspects of an epilepsy syndrome may be candidates for outcome assessment and possible description in labeling.
- Seizure-free days might represent a promising approach to long term studies. Definition of what constitutes a seizure-free days should be carefully described and discussed.

Non-seizure outcomes for focal epilepsy

Cognition

- Cognition and mood in patients with epilepsy is complex, since they can be influenced by underlying disease-related factors, non disease-related factors, ongoing ictal activity (potentially including inter-ictal spikes) and concomitant ASM medication
- Patient perception of cognition is heavily influenced by mood
- Proposed tools for testing cognition in epilepsy trials should be discussed in advance of implementation

Mood

- Mood disorders in epilepsy are multifactorial. Important factors include influence of underlying biology and concomitant ASMs. The impact of seizures and interictal activity can produce baseline variability.
- Family history of mood disorder is a strong predictor of mood disorder, and mood disorder as an adverse event related to use of ASM therapy. This information should be captured in any trial studying mood

- Studies of new therapies that improve mood in people with epilepsy may fail, because the sample size is determined based on efficacy outcome in the total cohort, but mood can only improve in subjects who have a mood disorder at baseline, which will be a significantly smaller subset. Subjects with mood disorder can be identified using scales like the MINI.
- Changes in seizures during the trial could also impact mood

Hot Topic: Long-term seizure outcomes

- Our family partners emphasized the difficulty of long-term seizure monitoring. Data from the subjects with focal epilepsy in the Human Epilepsy Project suggest that the majority of people will not track daily for the long term

- Alternatives to long-term daily tracking include:
    - Intermittent tracking
        - Disadvantage is people getting out of the habit of tracking
    - Tracking only “seizure free days”
        - Advantage: This accounts for both countable and “non-countable” seizures (eg absence, myoclonus).
        - Preliminary data suggests seizure-free days tracks with quality of life
    - Tracking “good days and bad days”
        - This also accounts for both countable and “non-countable” seizures
        - There would have to be significant work to determine if people understand the concept, and are able to distinguish seizures and their consequences from other reasons for a “bad day” (such as medication side effects

- Very long-term (years) of seizure diary counts are not likely to be required for safety assessments of gene therapies

A manuscript is in preparation, and planning is already underway for an in-person RRE meeting in 2025, with the topic to be defined soon. Learn more about the RRE here or email Caitlin Grzeskowiak, Vice President of Research and Innovation at cgrzeskowiak@efa.org.