2025 Research Roundtable for Epilepsy (RRE)

Measuring Seizure Impact Beyond Counting
April 24th and 25th, 2025

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 2025 RRE was held April 24th and 25th in Washington DC, convening researchers, people with lived epilepsy experience, companies with therapies in development for epilepsy as well as regulators from the FDA and others.

The meeting addressed the use of seizure counting as the primary determination of whether new therapies are effective. The meeting was comprised of 4 sessions:

- Session 1: Issues with seizure counting discussed the difficulties of counting seizures, including inaccurate diary counts, as well as substantial variability when counting certain seizure types.
- Session 2: EEG as Practical Alternative to Diaries addressed whether using EEG could lead to a more accurate count.
- Session 3: Alternatives to Diary Seizure Counting – Devices addressed the many devices available for seizure counting, and whether they would be useful for the purposes of a regulatory clinical trial.
- Session 4: Alternatives to Diary Seizure Counting – Seizure Outcomes discussed whether the absolute number of seizures, while an important outcome, was able to capture the impact of seizures, or whether it would be important to use other measures in tandem.

A summary of the discussion and conclusions are included below.

Issues with seizure counting by patient/observer report (seizure diary)

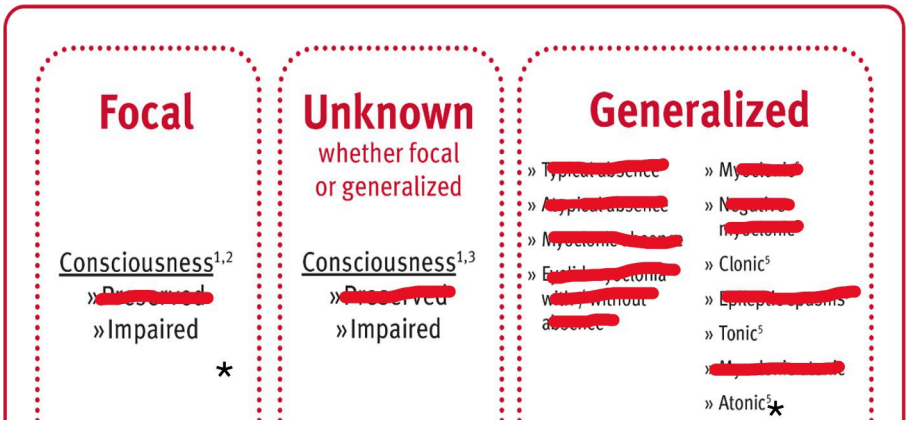
Some seizure types are easier to count, and are typically included in trials where the outcome measures are diary counted seizures. Other seizure types are considered "uncountable", and are not counted towards the primary endpoint of most clinical trials due to imprecision. Yet, "uncountable" seizures may contribute substantially to seizure burden in some individuals. Even for "countable" seizures, both over and underestimates of seizure counts are still a problem. Countable seizures assessed using seizure diaries, while not perfect, are usually adequate to demonstrate drug effect in trials. However, in some syndromes (e.g. Lennox-Gastaut syndrome) some individuals may have insufficient countable seizures to be enrolled in a trial and in other syndromes (e.g. absence epilepsy, myoclonic-astatic epilepsy) *only* uncountable seizures are experienced, excluding diary counting as a potential outcome measure.

Countable vs uncountable seizures:

- *Idiopathic generalized epilepsy:* countable seizures are generalized tonic-clonic seizures(GTC). Myoclonic and typical absence seizures, that are brief and may cluster are not considered countable.*Focal epilepsy:* countable seizures are those with observable features (focal with preserved consciousness(FPC) with observable features, focal with impaired consciousness (FIC), focal to bilateral tonic clinic(FBTC)). Non-observable FPC are not considered countable.
- *Developmental and Epileptic Encephalopathy (DEE):* Countable seizures include tonic/atonic with

loss of posture; focal with observable phenomena, and tonic-clonic seizures.

- Events that are brief, subtle, without clear onset/cessation (e.g., myoclonic, atypical absence, tonic/atonic without posture change), occurring in the presence of an impaired behavior baseline are not considered to be countable. Infantile spasms also cannot be counted accurately by diary.
- Factors that decrease countability, even for "countable" events include: lack of self-awareness, ambiguous beginning or end, events in clusters, high frequency events.



Accuracy of seizure diaries

- Daily entry in seizure diaries is difficult, and may not be sustainable for some people over longer periods. A new challenge for future trials is study of disease modification treatments that likely require long-term seizure counting (> 6 months).
- Seizure diaries used for trials may not allow for features that are considered useful in diaries for non-research use (such as free text notes, which can be problematic in a regulatory diary).
- Patients/caregivers are influenced in their tracking behavior by benefit/burden ratio: access to treatment, frequency and complexity of seizures, recall, emotional burden. A better understanding of long-term tracking behavior is needed.
- In some neurodevelopmental disorders (eg tuberous sclerosis, Rett syndrome, Angelman syndrome, SYNGAP1, GRIN-related DEE) some individuals may have frequent seizures, while others may have none at all. In this situation, requiring all subjects to report daily on a seizure diary may not be appropriate. Trials can be enriched for participants meeting minimal baseline seizure frequency, but enrollment may suffer. Designs need to account for for heterogeneity.
- Long-term alternatives to daily counting include: intermittent diary tracking, use of adaptive prompting for infrequent seizures, low burden approaches such as SMS and voice systems, and use of wearables or minimally invasive sensors.

EEG as a practical alternative to diaries

There may be alternatives to patient reported seizure, diaries. This session explored whether in some circumstances, and for some seizure types, recording seizures on EEG could be an alternative outcome measure for clinical trials.

- This would only be appropriate if there was a very high sensitivity and specificity of EEG recorded seizures in relation to clinical seizure occurrence. This may be true for some seizure types and may not be true for others.
- There may be "electrographic seizures" that are not clinically perceived by the patient. It is not always a given that reducing electrographic seizure burden results in clinical improvement (although the same can be said of seizure counting).

- Sensitivity and specificity depend on seizure type, setting (home, ambulatory, inpatient), timing of recording, and type of device (scalp, sub-scalp, intracranial).
- EEG at home may represent a burden (more or less, depending on the device) to patients and caregivers.

EEG & Typical absence seizures (TAS):

- There is an urgent need for an outcome measure for trials in typical absence, since patients and observers do not identify TAS accurately; however, most have clinical signs: pause/stare, motor automatisms, eye signs.
- Based on rigorous studies, in individuals with TAS, generalized spike and wave (GSW) discharges lasting 3 seconds or longer have a very high likelihood (>90%) of being clinical seizure events.
- Because a limited array EEG can detect TAS, wearable devices have great potential to be used as a trial outcome measure.

EEG & Focal seizures:

- There is variable in observability and countability (not reliable counts by patients/observers), but seizure counting by diary has been successful for trials.
- Focal seizure counting by scalp EEG is limited by spatial coverage and signal attenuation, but a high proportion of seizures having scalp EEG correlate. There may also be electrographic seizures seen on EEG that have no clinical correlate. Therefore, Ictal EEG-based counting may be an alternative but there are questions about feasibility and clinical meaningfulness.

EEG & Tonic-clonic seizures (TCS):

- Scalp EEG has high sensitivity for both focal onset and generalized onset TCC and low-moderate false positives due to artifacts (e.g., movement).
- Scalp EEG with limited electrode array has high sensitivity but modest specificity.

Seizures associated with DEEs:

- Video-EEG in EMU has highest sensitivity. EEG without video is subject to false positives and false negatives, and is not accurate enough to act as an outcome measure for trials at present.

Alternatives to diary seizure counting – Devices

There are many devices in development for seizure detection/counting. Some measure limited EEG array (either surface EEG or subscalp EEG) with or without other physiologic signals, while others rely on physiologic signals (eg motion, heart rate, skin galvanic conduction) to detect seizures. These offer potential for trials, but there are still a number of factors to be considered.

- If devices are used as a trial outcome, this may effect recruitment if some individuals prefer not to use them. Even if they are accepted, they should not represent a large burden in terms of wearability. Also, if a device needs daily charging, compliance to the device will need to be monitored to avoid missing data.
- Implantable devices can tract ictal and inter-ictal EEG activity, but cannot be implanted for the purpose of a trial (too invasive), so there may be initial lack of scalability, until a high number of people receive the device.
- Multi-modal Systems combining motion, HR, EEG, and electrodermal activity (e.g., EpiWatch, Empatica Embrace, are FDA-cleared for detection of TCC but not necessarily counting. Ability to detect other seizure types is limited. Video and Audio monitoring with AI can capture behavior during seizures and nocturnal events but are limited to home/hospital environments and trigger privacy concerns.

Non-EEG device pragmatics:

- Technology issues: Accurate capture of signal; barriers related to charging, durability, reliability, data fidelity and gaps; data transmission and storage; and data quality monitoring.
- Study participant issues: Compliance and acceptance (e.g., burden, visibility).
- Trial site issues: Comfort with technology and with providing support, IT security concerns.
- Sponsor issues: Increase trial complexity and expense, data ownership and confidentiality, site technical requirement limitations.

Alternatives to diary seizure counting – Seizure Outcomes

Two individuals who both experience the same number of seizures can have substantially different impact on their function. This can be due to the type of seizure, it's severity, and the post-ictal consequences. Of these, only seizure type is captured in a seizure diary, and that is not usually factored into the primary outcome of trials. In addition, uncountable seizures are not considered in the outcome, and these might account for a large portion of the burden of disease for some individuals, Therefore there is an urgent need for outcome measures that consider these factors.

Aspects of seizures that cause impairment include seizure symptoms (e.g. loss of consciousness, confusion), seizure duration (to recovery), symptom-related impact (e.g., limitations in household activities, impaired cognitive processing) and general impact (e.g., quality of life, depression). Other factors include type of seizures, aura, postictal state, timing of seizures, rescue medication burden.

Seizure severity scales:

- Seizure severity scales focus on measuring treatment-modifiable aspects that make seizures more or less burdensome (e.g., randomness, features that suggest spread/worsening). Some attempt to measure overall burden of severity and frequency, aiming at capturing totality of seizure impact, as well as uncountable or heterogeneous seizures present in DEEs and other neurodevelopmental disorders. Some focus on identifying characteristics and circumstances of an individual's "worst seizure". Available seizure severity scales include: Chalfont/Liverpool scale Seizure Severity Questionnaire (SSQ) (24-item "facilitated" interview; CGIs of seizure severity (SIGR).
- Impact scales include seizure burden, as well as other factors that effect quality of life such as medication burden and comorbidities. These include : Personal Impact of Epilepsy Scale (PIES) Desirability of Outcome Ranking (DOOR) Both were developed explicitly following FDA guidance.
- Epilepsy burden scales: These try to measure seizure frequency and impact, including "uncountable" seizures: Epilepsy burden scales include: Assessment of Seizure Free Days (simple count of any day with a seizure vs without) , SERIAS (SEizure Related Impact Assessment Scale). (Designed to assess days with no impact, partial impact, or high impact.)

Regulatory considerations

- Clinical benefit of an intervention is defined as "A positive effect of an intervention on how an individual feels, functions, or survives". This can be demonstrated as either a comparative advantage in treatment of the disease/condition; OR a comparative reduction in treatment-related toxicity. It is described in labeling in terms of the outcome of the interest measured.
- "Substantial evidence" needs to be documented, with endpoints (methods of assessment of patients' response) that are "well-defined and reliable" (validity, reliability), and are fit-for-purpose.
- Definition of COA (Clinical Outcome Assessment) , COA score, and Endpoint are found in PFDD draft guidance 3.
- Types of COAs: Patient-reported outcomes (PROs), Observer-reported outcomes (ObsROs), Clinician-reported outcomes (ClinROs), Performance outcomes (PerfOs).
- COA should be fit-for-purpose in its context of use: (appropriate for patient population and study design, measures a concept important to patients and clinically relevant, and can be communicated

in labeling accurately and interpretably.

- There is a Patient-focused drug development guidance series: Guidance 1 (Collecting Comprehensive and Representative Input), Guidance 2 (Methods to Identify What is Important to Patients), Guidance 3 (Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments), Guidance 4 (Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making).
- Roadmap to Developing a Fit-for-Purpose COA: PFDD draft guidance 3.

FDA recommendations:

- Follow the roadmap, which requires qualitative data collection on what is important to patients, caregivers, and clinicians anticipating heterogeneity in lived experience.
- Openness to discuss impact of daily function from seizures.
- Include all stakeholder perspectives.
- Leverage all data sources to explore assessment options/choices.
- Talk to FDA team early in the process and often.

Conclusions:

- Seizure diaries are widely used but present important limitations: underreporting and variable adherence. Diaries typically capture seizure counts but not severity, type, or impact, which are crucial for understanding treatment benefit.
- The seizure count is only one piece of the puzzle. Meaningful outcome assessment can benefit from capture of multiple dimensions: integrating type, severity, post-ictal effects, and patient-reported impact. There is an opportunity to evolve toward a multi-dimensional framework for seizure characterization in clinical trials.
- Devices (e.g., wearables) and EEG are promising future solutions, particularly for specific seizure types (e.g., EEG for absence, wearables for tonic-clonic). Technical validation (sensitivity/specificity), patient acceptance, adherence, and regulatory readiness remain hurdles. Existing FDA-cleared devices may be usable in trials, but investigational ones require careful validation.
- Seizure severity/impact is an important dimension of epilepsy that is currently infrequently incorporated into outcomes. Currently available scales (e.g., SSQ, Liverpool) are burdensome and underutilized. There is a need for non-burdensome, validated measures that reflect patient-experienced impact across seizure types, including uncountable ones. Example of a measure in development: SERIAS
- Ordinal or patient-weighted scoring systems may be explored for outcome measures for seizure type or impact (e.g., GTC = 3, focal aware = 1), with the caveat that such tools are justified with evidence and patient input. Regulatory adoption is contingent on rigorous validation and justification.

Learn more about the RRE here or email Eva Childers, Associate Director of Research (echilders@efa.org).