Worldwide Clinical Trials

Article

Beyond Seizure Counts: Expanding Endpoints in Pediatric Epilepsy Trials

Traditional clinical trials for pediatric epilepsy often rely on seizure frequency, as measured by seizure diaries, as the primary endpoint. However, seizure frequency does not always measure what matters most to patients and caregivers or capture the full spectrum of patient experiences in these indications. For example, many families are equally, if not more, concerned about other issues impacting the quality of life, such as gastrointestinal dysfunction, behavioral concerns, sleep disturbances, respiratory challenges, or the inability to understand their nonverbal child's wants or needs. Traditional outcome assessment tools often cannot capture changes in these domains because they lack the sensitivity to detect differences among individuals at the lower end of that trait or ability continuum. This is a pivotal issue requiring more comprehensive and patient-centered endpoints to address the heterogeneity of these disorders, such as Developmental and Epileptic Encephalopathies (DEEs), particularly as we learn more about the breadth of symptoms in diagnosed patients and the evolving comorbidities and challenges faced by those living with these diseases.

Juliane Mills, MPH, MS, Senior Director of Therapeutic Strategy at Worldwide recently hosted a webinar with three leading experts in the DEEs and epilepsy measures: Gabi Conecker, MPH, Executive Director and Co-Founder at Decoding Developmental Epilepsies; JayEtta Hecker, MS, Board Chair and Co-Founder at Decoding Developmental Epilepsies; Jessica Duis, MD, MS, Senior Medical Director in Clinical Development in Neurology at Neurocrine Biosciences and a clinician treating people with neurogenetic conditions through RareDiseaseDoc, LLC, and this article summarizes the key points discussed.

Trends in Endpoints for Epilepsy

Measuring epileptic seizures presents several challenges, such as the difficulty in accurately counting seizures, especially when they are not clinically apparent or when patients have multiple seizures per day. There have been innovations in the use of digital tools and quantitative EEGs in an attempt to move away from paper diaries. Still, even these digital tools are imperfect and do not fully address the challenges of accurate seizure counting. Quantitative EEG can be a tool to help understand brain activity, particularly the background brain activity related to the overall disorder, rather than just the epileptic seizures. Studies show this may be more relevant to understanding the cognitive and developmental impact of DEEs.[1] One trend in the type of endpoints for DEEs is a move away from seizures to more non-seizure outcome measures, especially with the emergence of many new disease-modifying therapies.[2]

This trend is driven, in part, by the FDA Patient-Focused Drug Development (PFDD) guidance to include patient experience data when evaluating new therapies. Yet most existing tools are not sufficiently sensitive to capture small but meaningful changes in profoundly disease-impacted individuals. The Inchstone Project, a global pre-competitive collaboration, is working to identify non-seizure outcomes prioritized by families across various etiologies and to adapt instruments to accommodate impairments in vision, motor skills, and cognition. Existing clinical tools that measure non-seizure outcomes lack the range and granularity needed to capture skills in those with DEEs or neurodevelopmental disorders (NDDs).

> The 21st Century Cures Act provides the impetus for robust inclusion of and reliance on patient experience data when evaluating the clinical benefits of new therapies. In response to the act, the FDA issued PFDD guidance to aid researchers and drug developers in designing clinical outcome assessments that provide optimal tests of a therapy's benefits.[2]

These diseases are characterized by severe to profound impairment in many functions critical to daily living and thus:

- Effectively exclude those with severe impairments from meaningful participation in clinical trials with any expectation of non-seizure benefits.
- Impede the ability of sponsors to evaluate disease-modifying therapies for the full range of the planned target population.
- Often leave trials unable to measure what is truly meaningful to patients and caregivers.

Individual disease communities (e.g., Angelman, Rett, CDKL5) are attempting to develop assessments capable of measuring change that clinical trials could use. Additionally, the Inchstone Project is working to create or adapt measurement tools that are sufficiently sensitive to demonstrate therapeutic efficacy in the small but meaningful non-seizure outcomes most important to families of those living with any of the DEEs, NDDs, and other severe diseases.

Another innovation is the use of individualized scaling, such as goal attainment scaling, which allows research participants to start from their baseline and progress at their own pace in a way that is meaningful to them. This approach focuses on the individual's progress throughout the observational or clinical trial. The goals are set based on the patient's initial condition and specific needs by the clinician and the individual or caregiver rather than using a one-size-fits-all approach. The intention is that this approach is more meaningful for patients with developmental epileptic encephalopathies, who have diverse developmental stages and needs.[3]

There is also a trend in rare disease to rely on global impression scales such as the co-primary endpoints used in the trofinetide study, which based approval on the Rett Syndrome Behavior Questionnaire and the Clinician Global Impression (CGI) scale.[4] CGI scales are commonly used to assess a patient's quality of life, depending on the experience of the individual clinician and the severity of the disease they have seen in their career. A clinician may sometimes barely see any difference because their experience is limited to patients on one end of the spectrum, presenting bias in the outcome of the measure depending on the clinician and consistency of completion.

Other trends discussed include:

- **Qualitative vs. Quantitative:** It is important to use both qualitative and quantitative measures in composite endpoints to capture a comprehensive picture of quality of life. This is increasingly feasible with the advancements in technology that facilitate these measurements. Entry and exit interviews when conducted systematically are important particularly in early phase trials to assess endpoints and clinically meaningful change during a trial.
- **Technological Advancements:** Advances in remote EEGs, video-based assessments, and digital health technologies have improved the ability to measure clinically meaningful outcomes more sensitively with repeated measures over a shorter period. As for specific tools in endpoint measures, there has been an increase in the use of remote video-based assessments and improvements in the use of wearables. Some studies currently use WiFi signals in the home to assess sleep, breathing, and even autonomic function without putting any device on the patient.
- **Ethical Concerns:** Ethical concerns about the invasiveness of some technologies in the home, such as cameras and wearables, were noted. Balancing practicality with the need for accurate measurements is crucial.
- **Practical Challenges:** When implementing assessments, it is crucial to acknowledge the practical challenges families face, such as touch sensitivity and reluctance to use invasive monitoring methods. This emphasizes the need for practical and acceptable measurement tools.

As noted by Dr. Duis, it can be challenging to connect these types of endpoints and how the patient feels or functions, for example, how a patient's step length impacts the day-to-day quality of life. There is also a need to define the minimally clinically significant difference (MCID) for each assessment. She explained that this is where composite endpoints can play a role and be used to convince regulators that the endpoint is meaningful to patients' lives and that a change in biomarker precedes positive qualitative changes.[5] For example, in lysosomal storage disorders, researchers have seen a change in glycosphingolipid levels and shown a correlative change in qualitative quality of life.[6]

Broadening the Scope of Clinical Trial Endpoints

The panel discussed innovative ways to capture the full impact of therapeutic interventions beyond seizures to ensure that trial outcomes resonate more accurately with patient well-being. JayEtta described the research supported by the Inchstone Project, led by a multidisciplinary group with extensive research credentials and publication history, as being able to conduct this work. Inchstone conducted a pilot study of 10 SCN2A-DEE patients with five instruments to understand caregiver priorities. This work illustrated the failure of most assessment tools to capture any of the endpoints that are meaningful to caregivers. For example, the assessment tools are not appropriate when they assume patients can move or they can talk, which some people with SCN2A are not able to do. This highlights the heterogeneity of some disorders, as seen in DEEs, which makes it challenging to select outcome measures that would suit the needs of the entire population.

From these important learnings, Inchstone has gone on to conduct broader surveys beyond SCN2A to capture data on priorities and meaningful change from more than 260 families across two dozen etiologies. The research has identified multiple domains that are meaningful to families, qualitative and quantitative. These domains include areas such as gross motor function, sleep, and autoimmune functioning — all of which are complexities separate from seizures. Just as importantly, the research has identified measurable increments of change across these domains.

JayEtta noted that this work provides outstanding evidence and consistency in the need among caregivers for improvements in communication as an endpoint and as a domain for assessment, which is independent of disease severity or diagnosis. She emphasized that communication should be the focus of new tools for development and where Inchstone is currently focusing its work.

Transforming Challenges into Actionable Research

The panel also shared their experiences in successful collaborative efforts between families, advocacy groups, and researchers to craft endpoints reflecting children's lived experiences with DEEs. Gabi shared that DEE-P Connections (The Inchstone project's home), in partnership with the Rare Epilepsy Network, held a cross-DEE listening session with the FDA in November 2024, with seven families representing eight DEE disorders. They received positive FDA feedback about their work across these diseases. Many panelists shared their positive impression that the industry and the FDA are increasing their flexibility to have a trial structure that includes more disorders when preclinical data suggests broader applicability.

All panelists agreed that industry collaboration is critically important to efforts to expand the scope of endpoint development beyond seizures and span across individual disorders. Gabi emphasized the importance of collaboration between patient advocacy organizations and industry partners, who provide funding and guidance and participate in industry advisory meetings to help guide the direction of The Inchstone Project and ensure its success. Gabi and JayEtta shared that Inchstone has a steering committee, a core research team, and an industry advisory panel from which they receive expertise, funding, and connections. In terms of best practices, they reported that Inchstone provides updates to the community and considers the needs of industry partners in terms of feasibility and timeline to bring adapted tools to fruition.

They emphasized the critical role of industry partnerships in developing and validating new clinical outcome assessments, highlighting the need for collaboration to test and implement these measures in clinical trials. Inchstone has fostered such strong partnerships to ensure their ongoing research can be applied to the industry's needs. JayEtta cited too many examples of families who saw a meaningful change in their family members during a clinical trial. However, because the change did not provide the evidence developers needed across a broader population, they discontinued the research and lost access to the medication. Inchstone is working hard to avoid that in the future through these partnerships and is eager to start using new endpoint measures in clinical trials as the ultimate validation test. They highlighted the importance of industry partners in helping to test new measures as exploratory or secondary outcomes in clinical trials, which is essential for their validation and eventual use in clinical practice.

For all the details, you can find the full webinar here.

References

1. Hipp JF, Frohlich J, Keute M, Tan WH, Bird LM (2021). Electrophysiological Abnormalities in Angelman Syndrome Correlate With Symptom Severity. Biol Psychiatry Glob Open Sci. 2021 Sep;1(3): 201–209. PMID: 34841387. PMCID: PMC8622755. doi: 10.1016/j.bpsgos.2021.05.003.
2. Berg AT, Ludwig NN, Wojnaroski M, Chapman CAT, Hommer R, Conecker G, Hecker JZ, Downs J. FDA Patient Focused Drug Development Guidances: Considerations for Trial Readiness in Rare Developmental and Epileptic Encephalopathies. Neurology. 2024 Jan 9;102(1):e207958. PMID: 38165374. PMCID: PMC10834124. doi: 10.1212/WNL.0000000000207958.
3. Sevic G, Knox K, George M, Evans L, Kaiser A, Paltell KC, Myers LS, Ludwig NN, Wonjnaroski M, Conecker G, Hecker J, Downs J, Chapman CAT, Berg AT. The Feasibility of Personalized Endpoints in Assessing Treatment Outcomes for Rare Diseases: A Pilot Study of Goal Attainment Scaling in SCN2A-Associated Developmental Epileptic Encephalopathy. Value Health. 2025 Mar;28(3):441-448. PMID: 39733836. doi: 10.1016/j.jval.2024.12.004.
4. Neul J, Percy AK, Benke TA, Berry-Kravis EM, Glaze DG, Marsh ED, Lin T, Stankovic S, Bishop KM, Youakim JM. Trofinetide for the Treatment of Rett Syndrome: A Randomized Phase 3 Study. Nat Med. 2023 Jun;29(6):1468-1475. PMID: 37291210. PMCID: PMC10287558. doi: 10.1038/s41591-023-02398-1.
5. Baracaldo-Santamaria D, Feliciano-Alfanso JE, Ramirez-Grueso R, Rojas-Rodrigues LC, Dominguez-Dominquez CA, Calderon-Ospina CA. Making Sense of Composite Endpoints in Clinical Research. J Clin Med. 2023 Jun 29;12(13):4371. PMID: 37445406. PMCID: PMC10342974. doi: 10.3390/jcm12134371.
6. Rossi A, Malvagia S, la Marca G, Parenti G, Brunetti-Pierri N. Biomarkers for Gene Therapy Clinical Trials of Lysosomal Storage Disorders. Mol Ther. 2024 Sep 4;3(9):2930-2938. PMID: 38850023. PMCID: PMC11403227. doi: 10.1016/j.ymthe.2024.06.003.