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SPECIAL REPORT

Operational definition of developmental and epileptic encephalopathies to underpin the design of therapeutic trials

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Abstract

Developmental and epileptic encephalopathies (DEEs) are the most severe group of epilepsies, characterized by drug-resistant seizures and developmental slowing or regression. DEEs encompass many epilepsy syndromes, although not all patients with a DEE can be classified into a specific syndrome. Our understanding of the etiologies of DEEs has been revolutionized with next-generation sequencing, with more than 900 genes implicated, in addition to structural causes. It is therefore now possible to consider precision medicine and novel therapeutic approaches for these devastating diseases with trials of repurposed and new drugs, including gene therapies. Trials are being designed to target either DEE diseases more broadly, specific DEE syndromes, or specific genetic DEEs. To serve this purpose, a clear operational definition of DEEs is needed to ensure that appropriate patients are selected for trials with precisely defined, targeted outcome measures. Herein we propose the operational definition of DEEs to set the stage for the development of DEE therapies.

KEYWORDS
developmental and epileptic encephalopathies, epilepsy, operational definition, precision medicine, trials

1 | INTRODUCTION

There is growing recognition of the urgent unmet need to improve outcomes for patients with the most severe group of epilepsies: developmental and epileptic encephalopathies (DEEs).[1] For the first time in the history of epilepsy, we are at a pivotal point where we can begin to tackle therapeutic management of DEEs in a targeted manner based on their neurobiology. Clear operational definitions of DEEs are needed to enable structured approaches to trials of novel antiseizure medications (ASMs) or repurposed therapies, including precision therapies, to ensure a robust framework to determine efficacy, safety, and tolerability.

The term "developmental and epileptic encephalopathy" was coined in 2017, encompassing two concepts, and building on the definition of an epileptic encephalopathy.[1] An epileptic encephalopathy refers to epileptic seizures in the setting of frequent epileptiform activity on electroencephalography (EEG) that result in developmental slowing or regression.[2] The developmental encephalopathy component of a DEE refers to the developmental consequences of the underlying etiology, which independently contribute to developmental impairment. If the DEE has onset in the neonatal period, it is usually impossible to tease apart these two components, that is, the developmental encephalopathy from the epileptic encephalopathy. However, if onset occurs in infancy or childhood, there may be a clear temporal separation between the developmental encephalopathy (slow development) and the adverse developmental consequences of a superimposed epileptic encephalopathy.

Although many well-established epilepsy syndromes are DEEs, a substantial number of patients with a DEE do not meet criteria for a known syndrome.[3–6] This means that recognizing and diagnosing a DEE is essential to ensure that patients are promptly offered appropriate therapies with the potential to ameliorate outcomes.

DEE syndromes are rarely homogeneous from an etiological perspective. One example, Dravet syndrome, is relatively homogeneous, as more than 90% of individuals have a pathogenic variant in *SCN1A*, the gene encoding the alpha-1 subunit of the sodium channel.[7] There are, however, numerous other genes that have been associated with Dravet-like phenotypes,[8] where subtle phenotypic features may aid distinction between different etiologies, such as the classical clustering of febrile seizures in *PCDH19* clustering epilepsy.[9]

Key points

- Developmental and epileptic encephalopathies (DEEs) are severe epilepsies with drug-resistant seizures and developmental slowing or regression.
- Over 900 genes and structural causes are linked to DEEs, thanks to next-generation sequencing.
- Precision medicine offers new hope, including repurposed drugs and gene therapies for DEEs.
- Trials target broad DEEs, specific syndromes, or genetic causes with precise outcome measures.
- A clear operational definition of DEEs is crucial for effective therapy development.

In contrast, the majority of epilepsy syndromes are etiologically heterogeneous such as Lennox–Gastaut syndrome, which has many acquired and genetic causes.[10] Where an acquired cause has been identified, it may also have an underlying genetic basis.[11] For the rare DEE syndrome of epilepsy of infancy with migrating focal seizures, more than 30 genes have been implicated including genes following dominant, recessive, and X-linked inheritance patterns, with a third of patients yet to have their etiology identified.[12]

There are >900 genes of major effect that cause DEEs,[13] in addition to acquired etiologies.[14,15] There is even greater complexity, however, as most genes are associated with a phenotypic spectrum, which is often determined by the functional impact of the pathogenic variant. One of the most important groups of genes implicated in DEEs are genes encoding ion channels. Their phenotypic spectrum is often explained by gain or loss of ion channel function,[16] or even mixed functional effects, which adds another layer of complexity with regard to treatment approaches. Thus, treatment approaches need to target the predominant functional effect and mitigate the risk that overtreatment may lead to the opposite functional phenotype, which may be just as concerning. This emphasizes the need for carefully constructed trials to detect whether novel therapies positively or negatively influence long-term outcomes.

With the marked increase in recognition and diagnosis of DEEs in the last decade, underpinned by molecular

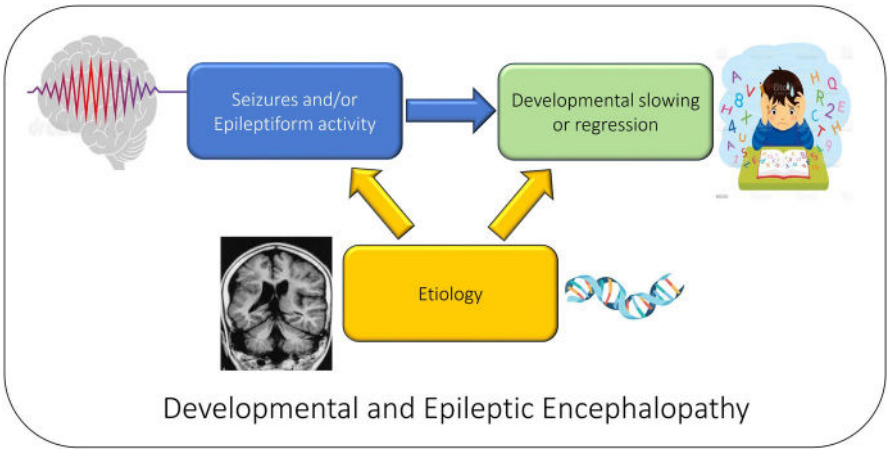

FIGURE 1 Critical components that define developmental and epileptic encephalopathy (DEE). These include: (1) the presence of seizures and/or epileptiform activity, which contribute to or exacerbate the neurological condition; (2) evidence of developmental slowing or regression, indicating an impact on cognitive and motor functions as a result of the condition; and (3) identification of an underlying etiology, which may include genetic, structural, metabolic, or other factors contributing to the disorder, and which play a major role on both epilepsy and developmental slowing or regression. This framework emphasizes the interplay between epileptiform activity and developmental impairment, underscoring the complexity of diagnosing and understanding DEE.

genetic insights, this group of diseases is considerably more prevalent than previously appreciated. A recent epidemiological study, based on EEG ascertainment in the Wellington region of New Zealand, found a cumulative incidence for DEEs of 1 in 590 children presenting under age 16 years, with those under age 3 years forming the largest group.[4] This confirmed findings of a prospective epidemiological study in Scotland that found an estimated incidence of DEEs of 86.1/100 000 children (95% confidence interval [CI] 72.7–101.3) with onset by 3 years of age.[17]

The diagnosis of DEEs has transformed in recent years with increasing understanding that treatment should focus not only on improving seizure control, but also on addressing all other features of these multimorbidity diseases. Morbidities include developmental delay and regression resulting in intellectual disability; psychiatric features including autism spectrum disorder, mood disorders, anxiety, and psychosis; gastrointestinal, musculoskeletal, respiratory, and cardiac manifestations, together with a considerably increased mortality rate.[18] Different morbidities may emerge in adult life and become the major focus of management, such as psychosis in women with *PCDH19* clustering epilepsy[19] and dysphagia, scoliosis, and incontinence in individuals with Dravet syndrome.[20] Novel therapies should aim to address both seizure and non-seizure outcomes, including all morbidities whenever possible.

Management of DEEs has centered around seizure type, adopting similar approaches to treatment of epilepsy used more broadly in the population. However, seizures in DEEs are often drug resistant and frequently encompass several types, including both generalized and focal seizures.[1] This means that broad spectrum agents are needed. Moreover, in some cases, we need to treat the ongoing epileptiform activity, not just the seizures. Although direct evidence is limited and likely to be syndrome specific, clinical practice suggests that treating epileptiform activity in DEEs may be associated with cognitive benefits and reduced seizure burden in some individuals. This is well illustrated by Landau–Kleffner syndrome, which falls under developmental and epileptic encephalopathy with spike–wave activation in sleep (DEE-SWAS), where only 70% of children have seizures,[6] but all show regression in receptive and expressive speech, and may regress in other domains. However, the impact of therapies of benefit in patients with DEEs often do not normalize the EEG, despite developmental gains.

The recent designation of breakthrough therapy status for Bexicaserin (LP352, Longboard Pharmaceuticals), with a trial for patients with any type of DEE, highlights a significant milestone: for the first time, a regulatory body (the U.S. Food and Drug Administration [FDA]) has endorsed a trial for all DEEs. This recognition underscores the pressing need for a consistent definition of DEE to guide emerging trials and therapeutic development, enabling the concept of a "basket" trial for all DEEs. As the field advances, we will need to establish a coherent framework that captures the characteristics of subtypes of DEEs for more targeted trials. A consistent definition of DEEs will pave the way for standardized trial designs, allowing comparability across studies.

Here, we operationalize the definition of DEEs to underpin an approach to designing clinical trials for

patients with DEEs, acknowledging that this is a work-in-progress as our understanding of these diseases and mechanisms continues to advance. Critically, the future therapeutic aim for the DEEs should be to address all features of the disease, a much broader remit than is usually considered for individuals with seizures. This is a stepwise process as we carefully examine the effects of novel treatments on both seizure and non-seizure outcomes.

2 | OPERATIONALIZING THE DEFINITION OF DEEs

A diagnosis of a DEE includes the following criteria (Figure 1):

1. Frequent seizures and/or EEG studies showing frequent epileptiform discharges
2. History of developmental slowing or regression
3. The underlying etiology also contributes to developmental impairment

2.1 | Frequent seizures and/or EEG showing frequent epileptiform discharges

Patients often have multiple seizure types, ranging from epileptic spasms to tonic, focal, and generalized seizures. Seizures are usually frequent and drug resistant; however, early in the disease, seizures may not always be frequent, as specific DEE syndromes may show a gradual evolution in seizure patterns and frequency.

EEG recordings may show abundant epileptiform discharges, which can be diffuse or multifocal, but can also be more prominent in specific regions of the brain. Distinct DEE patterns are recognized, such as hypsarrhythmia, burst-suppression, and periods of attenuation and slow spike–waves. However, in some DEEs, such as Dravet syndrome, early EEG studies may be normal or only subtly abnormal. A Dravet syndrome diagnosis can still be made early in life in the context of the appropriate clinical phenotype and etiology (e.g., recurrent hemiclonic or generalized tonic–clonic seizures and a *SCN1A* pathogenic variant) even when the EEG results are normal. Yet, in other DEE syndromes, such as early infantile DEE (EIDEE), epileptiform activity on EEG is expected early in the disease course. Subclinical ictal rhythms may also be observed. In certain cases, rigorous video-EEG analysis may be needed to distinguish between ictal and interictal discharges. Background EEG abnormalities are nonspecific and vary widely across DEEs; a normal background does not necessarily exclude a DEE diagnosis in a patient with established disease. Although EEG findings are supportive, they should be considered in the context of the patient's overall clinical picture and underlying etiology.

2.2 | History of developmental slowing or regression

Developmental slowing or regression is an essential component of a DEE, and arises due to the ongoing impact of the frequent epileptiform activity and/or seizures. The degree of slowing depends on the etiology; for some patients, it can progress slowly and quite insidiously over time, whereas for others, it may be evident soon after seizure onset or even before. Regardless of whether development is normal or delayed before seizure onset, DEEs are often slowly progressive diseases over time. Specific DEEs, such as Dravet syndrome, typically show developmental slowing from 1 to 2 years of age; however, the slowing often becomes evident before epileptiform activity is seen, due to the underlying *SCN1A* pathogenic variant. Although a change in the child's developmental trajectory (slowing or regression) is a key characteristic, it does not always occur in concert with epileptiform abnormalities on EEG or frequent seizures.

Conversely, children with an epileptic encephalopathy, but not a DEE, may ultimately have normal cognition. These patients have normal cognitive function and developmental milestones before the onset of seizures and show slowing during the time of their epileptic encephalopathy. Their development improves with resolution of the epileptic encephalopathy and their long-term outcome may ultimately be in the normal range.

2.3 | The underlying etiology also contributes to developmental impairment

The definition of a DEE encompasses the concept that the underlying etiology contributes to developmental slowing or regression, further impacted by both epileptic seizures and epileptiform activity. Even if seizures are controlled with medication or cease spontaneously, patients still exhibit developmental impairment over time. Well-established genetic etiologies, such as sodium and potassium channelopathies, cause intellectual disability and autism spectrum disorder without epilepsy or epileptiform activity, proving that these etiologies can cause developmental impairment in their own right. In 50% of cases, the etiology of DEEs is currently unknown; however, DEEs can still be diagnosed on the basis of clinical features.

Although a particular pathogenic variant in a specific gene may be highly predictive of a DEE, diagnosis of the electroclinical phenotype remains critical for an accurate DEE diagnosis. When the identified genetic variant is well established to cause DEE and has been associated frequently with a specific DEE phenotype, genetic findings can support an early diagnosis in the correct clinical context, even before the EEG shows the typical features or developmental slowing has occurred (e.g., *SCN1A* truncation variant in a 10-month-old baby with two episodes of febrile status epilepticus). However, for genes for which a variant is novel, the phenotypic spectrum of the gene is not well described, or the patient does not have classical features, a DEE diagnosis should not be made on the basis of a likely pathogenic variant.

3 | DESIGNING THERAPEUTIC TRIALS FOR DEEs

Trial design should capture all aspects of the disease and focus on those of greatest importance. Trial design should be tailored to the disease in question, the trial drug, and its mechanism(s) of action. Trial inclusion criteria will depend on the age of the patients being studied, their features (see Box 1), contraindications to the trial drug (e.g., endocrine abnormalities, past history of psychosis or depression) and their precise etiology, where relevant. DEEs are often slowly progressive in nature, with clinical, EEG, and neuroimaging features that evolve or plateau over time, and can usually be distinguished from neurodegenerative diseases where more rapid progression is seen, associated with neuronal death. Trials may target particular features of a DEE, such as seizure outcome or a specific morbidity, to determine effectiveness in treating that particular feature.

Ideally, precision therapies will directly address the underlying mechanism of the DEE in each patient. This will require different trial designs that examine outcomes more broadly. Some trials, such as gene therapies, will be challenging to execute as they will require careful, comprehensive, and long-term surveillance to ensure that improvement is robust, enduring, and that later adverse consequences do not emerge in adult life. Such trials are in early phases of development in the DEEs (see https://clinicaltrials.gov/), and currently have an appropriate focus on the detection of subtle gains in individuals who typically have profound to severe impairment. As commonly used assessment tools often have floor or ceiling effects, they do not identify subtle, yet meaningful, gains in children with DEEs. Many new tools are currently in development (e.g., Inchstone project).[21]

Although Class 1 evidence based on randomized placebo-controlled trials has been held as the gold standard, there is now considerable interest in other designs such as time-to-event,[22] n-of-1 studies,[23] and also comparison with natural history studies of historical cohorts (e.g., cerliponase alfa for CLN2 disease).[24] Such trials have different challenges in their design, such as how long a drug should be administered in n-of-1 studies to realistically show cognitive gains.[25] Given the complexity of DEEs, it is also possible that specific subgroups of patients with a phenotype or genotype may benefit from a trial drug, whereas other subgroups do not.

Novel trial designs are likely to introduce new ethical dilemmas. One example is the question of whether sham intracerebroventricular or intrathecal injections are ethical for placebo-controlled gene therapy studies. There is considerable concern about the risk of sudden unexpected death in epilepsy (SUDEP) in individuals with DEEs and it is conceivable that some novel trial designs may place patients at greater risk.

It is important to recognize that most patients with DEEs are taking multiple ASMs. There has been only limited work examining whether specific drugs have synergistic or antagonistic effects, although there are notable observational studies.[26,27] This aspect has understandably not been the focus of pharmaceutical companies, which are interested in showing efficacy of a specific compound. In the future, trial design may incorporate more rigorous analyses of concomitant drug regimens to understand the benefits or risks of combined therapies, to determine the optimal treatment paradigm for DEEs with specific etiologies.

4 | METHODOLOGICAL ISSUES REGARDING ACCURATE COUNTING OF SEIZURES

The most reliable way to count seizures has long been debated. Paper diaries have been the usual means, now being replaced by digital applications, but neither is perfect. Both require diligence in recording; however, families vary in their abilities to manage this reliably and over the longer term. The types of seizures that are counted in a trial vary according to the epilepsy in question. Most commonly, convulsive seizures have been counted but, more recently, countable motor seizures have been used as the primary outcome measure to determine efficacy.[28] This still leaves many potentially disabling seizures that have not been considered in DEE trials.

Although convulsive seizures appear more straightforward to count, they often have a predilection to occur in

BOX 1 Key features of developmental and epileptic encephalopathy (DEE), and clinical trial considerations including inclusion criteria and endpoints.

	Features	Details to consider
DEE definition		
	Frequent seizures (in most patients)	Frequency depends on DEE syndrome and/or etiology being studied
	Epileptiform activity on EEG	Amount and type depend on DEE syndrome and/or etiology being studied
	Development slowing or regression	
Possible inclusion criteria for trial		
	Age range of patients	Depends on trial design, trial drug, outcomes
	Seizures	Type(s)
		Methods of counting seizure Frequency
		Seizure duration
	EEG features – Epileptiform abnormalities	Frequency
		Type
	Developmental delay evolving to intellectual disability	Severity
		Cognitive profile
		ADHD
	Psychiatric features	Autism spectrum disorder
		Behavioural problems
		Psychosis
		Mood disorder
	Other systemic features	Depends on disease, trial drug (cardiac, musculoskeletal, gastrointestinal)
Possible core endpoints for trials		
	Change in seizure frequency	Reduction from baseline frequency, seizure-free days, time to event, depending on design
	Change in development	Slowing/gains/regression (improvement in adaptive functions)
	Frequency of use of rescue medication	Benzodiazepines
	Hospitalizations	Due to seizures, or to other medical problems
	Quality of life	Caregivers
		Clinicians
	Mortality	Causes (SUDEP, pneumonia, accidental, acute encephalopathy)

sleep and may be subtle and easily missed. With the advent of cameras in patients' bedrooms, more seizures are identified but can still be hard to detect if movements are not obvious. Tonic seizures, in particular, can occur very frequently, as in Lennox–Gastaut syndrome, and may simply comprise eye opening from sleep accompanied by a clear ictal rhythm on EEG. In reality, counting tonic seizures in sleep is fraught and only reliable with video-EEG monitoring, which is usually not available in an outpatient trial setting. Seizure counting is further compounded by patients showing considerable nightly fluctuation depending on the patient, their disease stage and seizure triggers, such as illness.

Other seizure types that are also challenging to accurately count include absence seizures (typical, atypical, myoclonic or with eyelid myoclonia[29]), myoclonic seizures, and epileptic spasms. EEG studies in children with childhood absence epilepsy show that the number of seizures is vastly underestimated by parental count compared

with video-EEG studies.[30] For absence seizures with eyelid myoclonia, families often stop "seeing" seizures, which may occur every few minutes with eye closure, every day, and come to be regarded as part of the patient's "normal functioning." However, each seizure is accompanied by generalized spike–wave activity on EEG, which interferes with a patient's cognition and learning. Various methods of counting absence seizures have been proposed, such as the number of seizures occurring in a set time period each day, for example, 15 min at dinner when the patient is closely observed, with no method proven to be adequate for a true count of seizure frequency.

Similarly, epileptic spasms, the key seizure type in infantile epileptic spasms syndrome and often seen in other infantile-onset DEEs,[5] can be hard to recognize. These very brief (<3 s) seizures usually cluster and may begin with a subtle movement such as a facial grimace or eye deviation, typically building in motor manifestations over one or a few minutes, before fading away. Parents may identify seizures when others do not recognize them. Trials typically count the number of clusters of epileptic spasms per day; this strategy of counting clusters may also be relevant to other diseases, such as *PCDH19* clustering epilepsy. Equally these seizure clusters can easily be missed in sleep, even with video cameras recording the patient. Isolated epileptic spasms can be even harder to document.

Furthermore, the aim of trials should be to stop all epileptic spasms, as a 50% reduction is not meaningful.[31]

Video-EEG studies for 1–2 days are expensive but can provide a more reliable estimate of seizure frequency, with the caveat that seizure frequency fluctuates in all individuals. Video-EEG monitoring improves accuracy by capturing all seizure types and providing continuous, objective monitoring, which is especially critical in patients with DEEs where atypical and subtle seizure types are common,[32] and parent- or caregiver-reported seizure counts may be inaccurate.[33] Long-term video-EEG studies in the setting of a drug trial are not viable for patients' lives; however, they are increasingly being used at specific time points in trials to provide an accurate and objective seizure count, typically as an exploratory endpoint. This strategy has not, however, always proven helpful, as counting absence seizures may be impossible due to an active interictal EEG.[34,35] Furthermore, the place of EEG studies in analysis of non-seizure outcomes is yet to be established, as it is unclear if findings will correlate with changes in cognition or other parameters.

5 | CONSUMER PERSPECTIVES

It is increasingly recognized that consumer-driven perspectives should be integrated in the trial design of new therapies.[36] It is crucial to prioritize the perspectives of patients and families given the multimorbidity nature of DEEs. Other medical problems, such as behavioral problems or intellectual disability, often eclipse seizures as their primary concern. Historically, clinical trials in epilepsy have focused on seizure frequency as the primary outcome. This approach may need to be reconsidered as trials of novel or repurposed compounds are devised with a focus on patient-centered outcome measures (PCOMs). PCOMs are personalized, structured, and measurable goals identified by individuals with complex health conditions or their carers, based on what matters most to them at the time.[37] The aim of PCOMs is to place patients, their families, and caregivers at the center of health assessment decisions, rather than leaving these assessments solely to clinicians.

With the tantalizing promise of precision approaches, many patient and family groups, physicians, and pharmaceutical companies are focused on developing robust clinical trials. Our operational definition of DEEs will guide trial designs facilitating appropriate recruitment. Looking to the future, endpoints for DEE trials should move from seizure outcomes alone to broader outcomes, incorporating many aspects of these multimorbid disorders, and applying a holistic lens to ensure that novel therapies improve patients' lives.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology: I.E.S., N.S., J.F., S.A., J.H.C., and K.D.V.; writing-original draft preparation: I.E.S. and N.S.; writing-review and editing: J.F., S.A., J.H.C., and K.D.V. All authors have read and agreed to the published version of the manuscript.

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Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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