International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

INPLASY2026110010

doi: 10.37766/inplasy2026.11.0010

Received: 3 November 2026

Published: 3 November 2026

**Corresponding author:**
María T. Acosta

acostam@nhgri.nih.gov

**Author Affiliation:**
Undiagnosed Diseases Program, National Human Genome Research Institute, National Institutes of Health.

# Genotype-informed outcome assessment for gene-targeted therapies in developmental and epileptic encephalopathies: a systematic review focused on Dravet syndrome

Esquerdo, MA; Giorgi, S; Zaragoza-Domingo, S; Aibar, JA; Acosta, MT.

## ADMINISTRATIVE INFORMATION

**Support -** No external funding. Internal resources of Dravet Syndrome Foundation Spain. Supported in part by the Intramural Research Program of the National Institutes of Health (NIH), USA.

**Review stage at the time of initial registration -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY2026110010

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 3 November 2026 and was last updated on 3 November 2026.

## INTRODUCTION

**Review question / Objective** Primary question: which clinical outcome assessments (COAs) are used to capture non-seizure outcomes in developmental and epileptic encephalopathies (DEEs), particularly Dravet syndrome (DS), how suitable are they, and how should genotype and therapeutic mechanism inform their selection to demonstrate disease modification? PICO. Population: people with DEEs of any genetic aetiology (DS, CDKL5 deficiency disorder, Lennox-Gastaut syndrome, SCN1A/SCN2A/KCNQ2/STXBP1-related encephalopathies, among others), plus caregivers and clinicians as informants; no age restriction. Intervention/exposure: the outcome-measurement approach (development, validation, adaptation or psychometric evaluation of COAs; qualitative/preference studies; trials of any therapy reporting at least one non-seizure COA; natural-history studies using non-seizure COAs). Comparator: conventional antiseizure-medication trials with seizure-only endpoints; DEE studies with validated or exploratory COAs; natural-history/baseline data contextualising COA performance. Outcome: caregiver/patient-reported priorities and perceived change; non-seizure domain results; psychometric properties (validity, reliability, responsiveness).

**Rationale** As gene-targeted therapies (antisense oligonucleotides, gene upregulation, gene replacement, precision small molecules) enter clinical development for DEEs, seizure frequency is no longer a sufficient measure of therapeutic success. Seizure control is often dissociated from developmental outcome, norm-referenced scores show floor effects in severely affected children, and families prioritise communication and other non-seizure domains. A systematic mapping of the COAs in use, their limitations, and how genotype, variant function and therapeutic mechanism should guide their selection is needed to support

Esquerdo et al. INPLASY protocol 2026110010. doi:10.37766/inplasy2026.11.0010 Downloaded from https://inplasy.com/inplasy-2026-11-0010/

demonstration of disease modification in clinical trials.

**Condition being studied** Developmental and epileptic encephalopathies (DEEs) are predominantly monogenic disorders in which seizures coexist with developmental impairment that seizures alone cannot explain. Dravet syndrome, caused mainly by loss-of-function SCN1A variants reducing NaV1.1 function in GABAergic interneurons (about 1 in 15,700 live births), is the paradigm: early-onset, treatment-resistant seizures with developmental slowing, intellectual and language impairment, behavioural and psychiatric difficulties, executive dysfunction, motor and gait abnormalities and sleep disturbance. Other DEEs considered include CDKL5 deficiency disorder, SCN2A-, KCNQ2-, STXBP1-, SYNGAP1-, GRIN-related disorders, FOXG1 syndrome, CNKSR2-related epilepsy-aphasia and Lennox-Gastaut syndrome.

## METHODS

**Search strategy** Databases: PubMed, Scopus and ClinicalTrials.gov. Period: 1 January 2020 to July 2026. Language: English. Four search strings combined terms for: (1) DEEs and relevant syndromes or genes (Dravet syndrome, CDKL5 deficiency disorder, Lennox-Gastaut syndrome, SCN1A, SCN2A, KCNQ2, STXBP1); (2) COAs, named instruments and measurement properties (e.g., floor effects, sensitivity to change); and (3) disease modification and advanced therapies (gene therapy, gene editing, antisense oligonucleotides, precision medicine). The complete search strings are provided in Supplementary Table S1.

**Participant or population** People with developmental and epileptic encephalopathies of any genetic aetiology (e.g., Dravet syndrome, CDKL5 deficiency disorder, Lennox-Gastaut syndrome, SCN1A/SCN2A/KCNQ2/STXBP1-related encephalopathies), and caregivers/families and clinicians/experts as informants. No age restriction.

**Intervention** Outcome-measurement approach: development, validation, adaptation, selection or psychometric evaluation of COAs (PRO, ObsRO, ClinRO, PerfO); qualitative/preference studies eliciting patient, family or clinician perspectives; trials of any therapy reporting at least one non-seizure COA; and natural-history studies operationalising non-seizure COAs. The COA must cover at least one non-seizure domain.

**Comparator** Conventional antiseizure-medication trials with seizure-only endpoints (for comparative endpoint-breadth analysis); DEE studies with validated or exploratory COAs; natural-history or baseline data contextualising COA performance.

**Study designs to be included** RCTs, open-label extensions, natural-history and prospective observational studies, qualitative/mixed-methods primary studies, and registered trial results.

**Eligibility criteria** Inclusion: peer-reviewed publications or trial-registry records, 2020 onward, in English. Exclusion: epilepsies without a developmental-encephalopathy component; non-DEE conditions; animal or in vitro studies (unless for COA instrument development); studies whose only outcome is seizure frequency or EEG; pharmacology/biomarker-only studies; case reports/series with fewer than 5 participants; editorials/opinion pieces (background only); abstracts without full data; pre-2020 records; grey literature without peer review or trial registration; studies with no comparator or baseline able to contextualise COA performance. Systematic reviews and meta-analyses were used only for background.

**Information sources** PubMed, Scopus and ClinicalTrials.gov. In addition, and separately from the systematic search, key primary studies and reviews on causal genes, variant mechanisms and therapies in development were reviewed to provide mechanistic context; these sources were not screened against the PICO criteria or counted as included studies.

**Main outcome(s)** Patient/caregiver-reported priorities, satisfaction or perceived relevance of outcomes; perceived change after treatment; trial expectations; non-seizure domain results (development, cognition, communication, adaptive behaviour, behaviour, motor function, sleep, quality of life, caregiver burden); and psychometric properties of COAs (validity, reliability, responsiveness, floor and ceiling effects). Reported narratively; no effect measures pooled.

**Additional outcome(s)** Position of non-seizure COAs in the endpoint hierarchy of interventional and registered trials; relationship between seizure control and developmental outcome; placebo-related effects; and mapping of genes, variant mechanisms, therapeutic approaches and candidate COAs.

**Data management** Records were entered into a screening database (Supplementary Table S2).

Esquerdo et al. INPLASY protocol 2026110010. doi:10.37766/inplasy2026.11.0010 Downloaded from https://inplasy.com/inplasy-2026-11-0010/

Each PICO criterion was rated met, uncertain or not met at title/abstract screening. A generative AI assistant (Claude Opus 5.5, Anthropic) proposed provisional ratings and helped organise and summarise included articles; M.Á.E. reviewed every proposal and made all initial inclusion decisions, and the tool excluded no records independently. Summaries were checked against the primary sources by the authors.

**Quality assessment / Risk of bias analysis** Study quality and certainty of evidence were not graded.

**Strategy of data synthesis** Narrative synthesis, guided by PRISMA 2020, because eligible records included psychometric, qualitative, natural-history, interventional and trial-registry sources. Effect estimates were not pooled. Findings were organised by domain, instrument and causal gene, and complemented by a narrative synthesis of the genetic architecture of DEEs and of therapeutic mechanisms to build a gene-mechanism-therapy-COA map.

**Subgroup analysis** COA findings were interpreted by the causal gene of each study population (e.g., SCN1A, SCN2A, KCNQ2, STXBP1, CDKL5). No formal subgroup analyses were performed.

**Sensitivity analysis** Not applicable. No quantitative synthesis was performed.

**Language restriction** English only.

**Country(ies) involved** Spain; United States.

**Other relevant information** Review conducted following PRISMA 2020. The completed PRISMA checklist and Supplementary Tables S1-S4 are available with the manuscript.

**Keywords** developmental and epileptic encephalopathy; Dravet syndrome; clinical outcome assessment; disease modification; gene therapy; antisense oligonucleotide; neurodevelopment; SCN1A; genotype-phenotype correlation; endpoint.

**Dissemination plans** Submission of the manuscript to a peer-reviewed open-access journal; sharing with the Dravet and DEE patient and family communities, clinicians, researchers and trial-readiness consortia.

**Contributions of each author**

Author 1 - Miguel Ángel Esquerdo - Methodology, formal analysis, investigation, data curation, original draft, visualisation.
Email: maesquerdor@gmail.com
Author 2 - Simona Giorgi - Conceptualisation, methodology, independent reassessment of included records, writing (review and editing), supervision, project administration.
Email: simona.giorgi@dravetfoundation.eu
Author 3 - Silvia Zaragoza-Domingo - Writing (review and editing), supervision.
Email: szaragoza@psyncro.net
Author 4 - José Ángel Aibar - Writing (review and editing), project administration.
Email: jaibar@dravetfoundation.eu
Author 5 - María T. Acosta - Conceptualisation, writing (review and editing), supervision.
Email: acostam@nhgri.nih.gov

Esquerdo et al. INPLASY protocol 2026110010. doi:10.37766/inplasy2026.11.0010 Downloaded from https://inplasy.com/inplasy-2026-11-0010/