Received: 19 December 2025 | Revised: 31 January 2026 | Accepted: 2 February 2026

DOI: 10.1002/epi.70152

Epilepsia®

RESEARCH ARTICLE

Evolution of the European Medicines Agency clinical guidelines for epilepsy drug development between 2010 and 2025: A comparative analysis by the ILAE Task Force on Regulatory Affairs

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Abstract

Objective: The latest European Medicines Agency (EMA) guideline on the clinical investigation of medicines to treat epileptic disorders was adopted by the EMA Committee for Medicinal Products for Human Use in 2025. We compared this guideline with the previous version (2010), highlighting areas where significant revisions were introduced.

Methods: The 2025 and 2010 versions of the guideline were systematically analyzed to identify significant modifications.

Results: The latest EMA guideline incorporated terminology from the 2017 International League Against Epilepsy (ILAE) classification of seizures and epilepsy and the 2022 classification of syndromes and replaced the older term "antiepileptic drug (AED)" with "antiseizure medication (ASM)." Recommendations for add-on studies in common epilepsies have remained substantially unchanged, the main revision being the acceptability of the time-to-event design also for confirmatory trials, provided it is not the only design in the clinical development plan. A major novelty is the feasibility of extrapolating data from add-on trials to the monotherapy indication, provided specific conditions are met. Guidance on pediatric ASM development has been expanded, addressing extrapolation of efficacy from data in adults and older children and options for studies in developmental and epileptic encephalopathies and other rare epilepsies. Compared with the previous guideline, greater emphasis is placed on nonseizure outcomes, including functional, quality of life, and patient-reported outcomes. Two new sections have been introduced, addressing studies in neonates and clinical trials in status epilepticus and other seizure emergencies. Options for innovative

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designs, including registry-based studies, are also discussed in situations where randomized controlled trials are unfeasible.

Significance: The updated guideline reflects the changing scenario in epilepsy treatment development, with a greater focus on pediatric epilepsies, rare epilepsies, and other indications with high unmet needs. The updates also reflect the contribution during the consultation process by a wide range of stakeholders, including the ILAE Task Force on Regulatory Affairs.

KEYWORDS

antiseizure medications, clinical trials, drug development, epilepsy, regulatory science, seizures

1 | INTRODUCTION

Over the past decades, the development of antiseizure medications (ASMs) has evolved. A crowded market for the common epilepsies has led to drug development focusing on new indications. Regulatory guidance has evolved in parallel. The first European Medicines Agency (EMA) guideline on the clinical investigation of medicinal products in the treatment of epileptic disorders came into operation in May 2001, [1] and a revised version was enacted in August 2010.[2] The latest version (Rev. 3) came into effect in September 2025[3] and was finalized after a 7-year process involving public consultation with different stakeholders. The Task Force on Regulatory Affairs of the International League Against Epilepsy (ILAE; https://www.ilae.org/about-ilae/committees-task-forces-and-advisory-commissions/regulatory-affairs-task-force) has been part of this process, through preparatory meetings addressing pediatric epilepsies, adult epilepsies, and epilepsy syndromes, followed by the participation of several members in the public roundtable held in January 2024. In addition, the Task Force was invited, along with other stakeholders, to provide comments via a dedicated online consultation platform.

This paper provides a comparative analysis of the earlier version (Rev. 2)[2] and the 2025 version (Rev. 3)[3] of the EMA guideline. We highlight how regulatory thinking has adapted to recent challenges in developing treatments for epilepsy. We discuss how the ILAE Regulatory Affairs Task Force contributed to this process and to important conceptual changes incorporated in the revised guideline. A complete reading of the EMA guideline documents remains essential to fully understand their content.

Key points

- The 2025 revision of the EMA guideline on epilepsy drug development incorporates terminology from the 2017 ILAE classification of seizures and epilepsy and from the 2022 classification of syndromes.
- For add-on studies, the time-to-event design may be accepted for confirmatory trials. Of note, data from add-on trials can be extrapolated to the monotherapy indication, provided specified conditions are met.
- Guidance on pediatric ASM development has been expanded, addressing extrapolation of efficacy data from adults and older children and studies in rare epilepsies, with greater emphasis on nonseizure outcomes.
- Two new sections have been introduced discussing guidance for studies in neonates and clinical trials in status epilepticus and other seizure emergencies.
- Overall, the guideline updates reflect the changing scenario in epilepsy treatment development, as well as the contribution provided during the consultation process by a wide range of stakeholders, including the ILAE Task Force on Regulatory Affairs.

2 | MATERIALS AND METHODS

We examined the most relevant differences between the second (Rev. 2)[2] and the third revision (Rev. 3)[3] of the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders published by the Committee for Medicinal Products for Human Use (CHMP). The CHMP is the EMA committee responsible for the scientific evaluation of medicinal products and for incorporating new scientific evidence into regulatory guidance for the development of ASMs.

Both documents were systematically analyzed to identify all significant modifications introduced in the 2025 version (http://www.ema.europa.eu/).

This analysis was conducted through a structured, multistep process involving meetings of the ILAE Task Force on Regulatory Affairs. First, a global comparison of both guideline versions was performed to identify newly introduced sections, concepts, or requirements that were absent from the previous version. Second, corresponding sections present in both versions were compared in detail to assess modifications, clarifications, or shifts in emphasis. These analyses were subsequently discussed among Task Force members to reach a shared interpretation of the changes. Based on these discussions, the manuscript was drafted to provide a structured and critical synthesis of the identified differences.

3 | RESULTS

3.1 | General structure and main scope

The 2010 guideline primarily focused on the investigation of ASM effects on seizures in adults with focal epilepsies and in selected epilepsy syndromes. It also included sections on drug development for pediatric epilepsies and epilepsy in the elderly. Development of ASMs in epilepsy syndromes other than focal epilepsy was encouraged, noting that "as trial experience is rare, in general no specific recommendation" could be made. No specific recommendations were provided on studies in neonatal seizures, for which CHMP scientific advice was suggested. Less than three lines addressed studies in status epilepticus (SE).

The 2025 revision broadens the scope to include the investigation of ASMs in developmental and epileptic encephalopathies (DEEs), seizures in the neonatal period, and SE. The section on pediatric epilepsy has expanded from 507 words in the 2010 version to 1956 words in the current guideline. The section on studies in the elderly was expanded to a much lesser extent (341 words vs. 262 words in the 2010 version). The 2025 revision also incorporates in greater detail the need to explore nonseizure outcomes, including cognitive, neuromotor, behavioral, and quality of life outcomes.

The structure of the 2025 guideline remains broadly similar to the 2010 version (Table 1). The methodology of clinical studies in Section 4.5 (Strategy and Steps of the Development. Methodology of the Clinical Studies) of the 2010 version is now redistributed within a broader section dedicated to study design (Section 6). Studies in pediatric and elderly populations (Subsections 4.2.4 and 4.2.5 in the 2010 version) are now addressed under a distinct heading (Table 1).

3.2 | Terminology

The 2010 version was mainly based on pre-2017 ILAE seizure classification and included terms such as "primary generalized tonic–clonic seizures" and "secondary generalized seizures." The revised version fully integrates the 2017 ILAE seizure classification, adopting terms such as "focal onset seizures," "generalized tonic–clonic seizures," and "focal to bilateral tonic-clonic seizures." Concepts from the 2022 ILAE syndrome classification have not been fully incorporated,[4] but DEEs are now recognized as a group of disorders with distinct nosological characteristics.

Terminology for medicinal products has also evolved. The term "antiepileptic drugs (AEDs)" used in the 2010 guideline has been replaced by the term "antiseizure medications (ASMs)" in alignment with current ILAE recommendations.[4,5]

3.3 | Recommendations that have remained substantially unchanged since 2010

As in 2010, the revised guideline stresses the importance of randomized, double-blind, placebo-controlled trial designs and the requirement for seizure type-specific evaluation. No changes have been made to the recommendations concerning use of add-on studies in assessing initial efficacy, the preference for parallel-group designs (at least for pivotal trials), and the use of responder rate (percentage of patients with a decrease in seizure frequency by at least 50% vs. baseline) as primary endpoint.

Suggestions for exploratory studies also do not differ between the 2010 and the 2025 versions, with emphasis on flexibility. Examples cited with virtually identical wording in both versions include "randomized placebo-controlled parallel or cross-over studies, enrichment designs, controlled studies in patients ... subjected to a pre-surgical evaluation program, and open add-on studies, among others."[2,3] Both versions mention the electroencephalographic (EEG) photoparoxysmal response, or the study of the effects on interictal EEG epileptic discharges, as examples of models for obtaining a preliminary estimate of clinical efficacy.[2,3]

In both guideline versions, seizure counts are recommended as the primary measure of treatment efficacy. For hard-to-quantify seizures (e.g., absences), methods such as EEG recording are recommended. The 2025 revision suggests that, when seizures are infrequent or EEG monitoring is not feasible, alternative metrics, such as seizure-free days, may be used. This suggestion is not entirely novel, because the 2010 guideline also cited the possibility of assessing days without myoclonic seizures as an efficacy measure in patients with idiopathic generalized epilepsies.

TABLE 1 Tables of contents of the 2010 and 2025 EMA guidelines on clinical investigation of medicinal products in the treatment of epileptic disorders.

2010 EMA guidelines (Rev. 2)	2025 EMA guidelines (Rev. 3)
1. Introduction (background)	1. Introduction (background)
2. Scope	2. Scope
3. Legal basis	3. Legal basis and relevant guidelines
4. Main text	4. Patient selection
4.1 Selection of the seizure type and epilepsy syndrome	4.1. Study population and selection of patients
4.2 Specificity of clinical trials in epilepsy	4.2. Selection of seizure types and epilepsy syndromes
4.2.1 Add-on studies	5. Assessment of efficacy
4.2.2 Monotherapy studies	5.1. Efficacy criteria/treatment goals
4.2.3 Dosage	5.1.1. Add-on trials
4.2.4 Development of AEDs in children	5.1.2. Monotherapy trials
4.2.5 Development of AEDs in the elderly	5.1.3. Add-on and monotherapy trials
4.3 Assessment of efficacy	5.2. Methods to assess efficacy criteria
4.3.1 The assessment of efficacy should be based primarily upon seizure frequency/occurrence	6. Study design
4.3.2 Other methods to assess efficacy	6.1. Non-clinical data
4.4 Statistical analyses	6.2. Pharmacology studies
4.5 Strategy and steps of the development: methodology of the clinical studies	6.2.1. Pharmacokinetics
4.5.1 Pre-clinical data	6.2.2. Pharmacodynamics
4.5.2 Pharmacodynamic human data	6.2.3. Interactions
4.5.3 Pharmacokinetics	6.3. Therapeutic studies
4.5.4 Interactions	6.3.1. Exploratory and dose finding studies
4.5.5 Methodology of clinical studies	6.3.2. Confirmatory studies
4.5.5.1 Study population and selection of patients	6.3.3. Statistical analyses
4.5.5.2 Therapeutic exploratory studies	6.3.4. Specific cases
4.5.5.3 Therapeutic confirmatory studies	7. Safety aspects
4.5.5.4 Specific cases	7.1. Specific effects
4.6 Safety aspects	7.2. Long-term effects
4.6.1 General considerations	7.3. Safety endpoints
4.6.1.1 Exacerbation of seizures	7.3.1. Exacerbation of seizures
4.6.1.2 CNS adverse events	7.3.2. CNS adverse events
4.6.2 Long-term safety	8. Studies in special populations
4.7 Conditions for registration	8.1. Studies in pediatric patients
5. References	8.1.1. Development of ASM in children
	8.1.2. Development of ASM in neonates
	8.2. Studies in the elderly patient
	9. References

Abbreviations: AED, antiepileptic drug; ASM, antiseizure medication; CNS, central nervous system; EMA, European Medicines Agency.

Recommendations for preclinical studies are brief in both versions and highlight the importance of understanding mechanisms of action to predict efficacy across seizure types and potential side effects. They also highlight the importance of evaluating efficacy in different preclinical models and, for indications <4 years of age, the need to assess neurotoxicity in the developing rodent brain.

Requirements for pharmacokinetic and drug–drug interaction studies also remain unchanged, with emphasis on the need for a comprehensive pharmacokinetic characterization and the assessment of plasma concentration–response relationships. Both guideline versions require assessment of interactions with concomitant ASMs, oral contraceptives, alcohol, and central nervous system (CNS)-active drugs. In addition, the use of neuropsychological tests is recommended for compounds with potential sedative or CNS depressant effects.

Both guidelines emphasize the need for careful safety assessment, including seizure worsening and exacerbation of cognitive, behavioral, mood-related, and neuromotor symptoms, with particular attention to vulnerable populations such as children and older people.

3.4 | Novelties introduced in the 2025 guideline

3.4.1 | Novel trial designs for assessment of efficacy

Assessment of responder rate over a maintenance period of at least 12 weeks remains the recommended primary endpoint for add-on trials. However, alternative approaches designed to shorten prolonged exposure to

placebo or ineffective treatments can now be considered. Specifically, the time-to-event design is now considered as potentially acceptable also for confirmatory studies, even though it is not recommended as the sole study design in the clinical development plan.

3.4.2 | Monotherapy indication

The 2025 revision introduces a shift in the regulatory approach to the granting of a monotherapy indication. Before 2025, the recommended approach was the conduct of "randomized, double-blind active-controlled trials aiming to demonstrate at least a similar benefit/risk balance of the test product as compared to an acknowledged standard product at its optimal dose" in newly or recently diagnosed patients.[2,3] The recommended trial duration was at least 1 year, with the proportion of patients remaining seizure-free for at least 6 months (excluding the dose titration period) as the primary efficacy endpoint. It was acknowledged that "assay sensitivity might be a problem," but it was felt that "stepwise fixed dose increments based on response may be an option to guarantee assay sensitivity."[2] In the 2025 guidelines, concerns about assay sensitivity in these studies are prominently emphasized. Specifically, it is pointed out that "in practice, seizure recurrence in these trials has been low, so that the majority of the patients remain seizure-free for the duration of the trial. These trials therefore often lack or have limited assay sensitivity, and therefore results are difficult to interpret."[3]

The updated guidelines now state explicitly that "on a case-by-case basis, it may be justified that a monotherapy trial is not necessary to support a monotherapy indication."[3] This means that efficacy observed in add-on studies may, under certain conditions, be extrapolated to the monotherapy setting. Whether such extrapolation is appropriate depends on various factors, including the ASM mechanism of action and the robustness of efficacy data from add-on studies, such as the magnitude of effect, exposure–response relationships, and the consistency of response regardless of concomitant ASMs.

When extrapolation of efficacy is not justified, the 2025 guideline proposes a "randomized, standard-of-care controlled, open-label study of at least 12 months' duration with treatment retention rate as the primary endpoint."[3] Noninferiority trials, as recommended in the 2010 guidelines, may also be considered. To address assay sensitivity, strategies include enrolling patients with high baseline seizure frequency or extending follow-up. The guideline further notes that trial objectives and endpoints may vary by population. The need for outcome data in patients converting from add-on therapy to monotherapy is also emphasized, as in the previous guideline.

3.4.3 | More detailed section on studies in pediatric populations

The 2010 guideline stipulated that, for focal epilepsy, efficacy established from trials in adults could be extrapolated to children older than 4 years after adjusting for pharmacokinetic variation. In contrast, for infants/children aged 1 month to 4 years, video-EEG monitoring studies were required. For other pediatric syndromes, large exploratory studies stratified by age or syndrome were recommended, aiming to generate early data on pharmacokinetics, safety, and efficacy. For safety, it was mentioned that at least 100 children should be followed for at least 1 year, evaluating developmental characteristics such as behavior, cognition, growth, and endocrine function.

For focal epilepsies, the 2025 guideline reiterates the feasibility of extrapolation of efficacy data from studies in adults referencing International Council for Harmonisation guideline E11A,[6] although a cutoff at 4 years of age is no longer mentioned. It also mentions that for focal seizures and some nonfocal seizure types such as generalized tonic–clonic seizures associated with idiopathic generalized epilepsies, "once efficacy has been shown in the older age-subsets, short-term assessment of response by using diary and/or video EEG/EEG monitoring only may be sufficient as supportive of efficacy."[3]

Requirements on use of video-EEG monitoring in the younger population have evolved. Video-EEG is recommended, when appropriate, for the identification and confirmation of diagnosis. For patients aged 1 month to less than 4 years, EEG and video-EEG are cited as tools to document seizure reduction, mainly when manifestations are subtle. Wearable devices for seizure detection could be used if validated. Of note, median percent seizure reduction would be acceptable as a primary endpoint for studies in rare epilepsies, provided that responder rates are included as a secondary endpoint. Time-to-event designs with variable exposure to exposure could also be acceptable.[7]

For epilepsy syndromes, demonstration of efficacy requires randomized controlled trials, and the suggestion is made that dose selection could be facilitated by pharmacokinetic modeling aimed at ensuring exposures similar to those associated with efficacy in adults with other seizure types. The 2025 guideline also includes a discussion of ASM development for DEEs, where adjustments in trial design and endpoints may be required due to the heterogeneous manifestations and rarity of these disorders. In particular, the guideline mentions that "for a rare specific DEE subgroup, a N-of-1 study design (i.e. multiple crossover study within one subject with 1-2 placebo treatment periods), in a limited number of subjects might be acceptable in support of efficacy."[3] Interestingly, the guideline

also addresses disease modification, mentioning that this would require demonstration "that the treatment affects the underlying pathophysiology, that it has a beneficial effect on seizures and improves neuromotor, cognitive and behavioral development."[3] Such a demonstration would be dependent on the availability of long-term comparative data, and scientific advice from the CHMP is recommended.

3.4.4 | More detailed section on studies in the elderly population

The 2010 guideline emphasized that efficacy and safety of ASMs in older people may differ significantly from those in younger adults due to distinct etiologies, altered pharmacokinetics, and increased susceptibility to adverse effects. Section 8.2 of the 2025 guideline provides more detail on these points and recommends including an adequate number of elderly patients in phase III trials, differentiating between individuals with long-standing epilepsy and those with recent onset epilepsy due to underlying diseases such as stroke. Although the core recommendations remain largely unchanged, it is suggested to seek CHMP scientific advice when considering alternative study designs to extrapolate efficacy and safety data from pivotal trials in younger adults to the elderly.

3.4.5 | Newly introduced section on neonatal seizures

Developing ASMs for neonates presents unique challenges. Intravenous formulations are required to ensure timely and reliable administration. Eligible neonates for clinical studies include those with EEG-confirmed or clinically identifiable repeated seizures, or those at high risk due to conditions such as hypoxic–ischemic encephalopathy, stroke, or genetic etiologies, typically from 34–35 weeks of gestation to 28 days postnatal age. Inclusion of more premature infants should be considered only after safety and pharmacokinetic data have been established in term neonates. Continuous multichannel video-EEG is essential for accurate seizure detection, as electrographic seizures may lack clinical correlates. Involving at least one central reader to confirm the EEG interpretation is recommended. Seizure burden should be defined as duration of seizure activity in the EEG over a predefined period. The evaluation should last no less than 12–24 h and continue until the patient has been seizure-free for a predefined interval, preferably at least 12–24 h. In addition, any clinical observable motor seizures should be evaluated, and patient/caregiver-reported outcomes may be considered.

Clinical trials should ideally include newborns with seizures resistant to first-line treatment and apply seizure burden thresholds as entry criteria. The primary outcome should be seizure freedom over a predefined period, with subjects dropping out prematurely or requiring rescue therapy considered nonresponders. Etiological diversity and the potential impact of interventions such as therapeutic hypothermia must be balanced across study arms. Studies focused on a single etiology may be preferred for confirmatory trials. Randomized comparative controlled trials are preferred, and although historical or registry-based controls may be considered, they require strict methodological justification and matching criteria. Evidence of efficacy requires demonstration of superiority over the comparator groups.

Safety is particularly important in neonates. A minimal follow-up period within the clinical study of 30 days after the final dose is recommended to assess the persistence of treatment effects. In addition, specific safety assessments should monitor potential short- and medium-term adverse effects. Long-term evaluation requires follow-up of at least 18–24 months, addressing neuromotor, cognitive, and behavioral development.

3.4.6 | Newly introduced section on SE

A new section (6.3.4) on SE[8] has been introduced, emphasizing the need for separate clinical development in this indication. The importance of prompt treatment, typically via intravenous or intramuscular routes, is highlighted. Clinical trials should predefine clear criteria for rescue treatment and the time points at which treatment should be initiated, depending on the type of acute event. If the treatment under investigation is a drug–device combination, efficacy and safety need to be demonstrated for the integral medicinal product as used by the intended user population.

In line with the current view of experts,[9] the guideline distinguishes three clinical scenarios: treatment of the acute SE, prevention of recurrence of SE, and treatment and prevention of (super-) refractory SE.[10,11] For each condition, both trial design and study endpoints are different, and stratification by prognostic factors, such as etiology,[12] is recommended. Clinical trials should be designed to show noninferiority or superiority to an appropriate active comparator (benzodiazepines if first line; fosphenytoin, phenobarbital, or phenytoin if second line).

The need for clearly defined endpoints, such as seizure cessation within a specified time frame, is highlighted. For acute SE, persistent seizure cessation should be the primary endpoint. For the prevention of seizure recurrence,

the primary endpoint should be the absence of recurrence after the time at which the effect of the treatment that terminated the seizure had ceased. For refractory and super-refractory SE, functional outcomes are recommended as the primary endpoint. The guideline also clarifies that for other seizure emergencies, including prolonged seizures that do not qualify as SE or acute repetitive seizures, studies should follow the principles for trials in SE, with similar endpoints.

4 | DISCUSSION

The 2025 EMA guideline includes novel content that reflects the changing scenario in epilepsy drug development, with a greater focus on treatments for rare epilepsies and pediatric indications where unmet needs are greatest.[13–15] The guideline also incorporates the modern classification of seizures and epilepsies.[16–18] It addresses several critical issues related to ASM development and trial design that have been discussed within the epilepsy community.[13,19–23] Most revisions introduced represent welcome developments and reflect the regulators' attention to scientific advances as well as their willingness to engage in consultation with all relevant stakeholders. The ILAE Regulatory Task Force and other health care professionals and scientists associated with the ILAE were active participants in this process.

Among the changes incorporated in the 2025 guideline (Table S1), several novelties require special comment. Use of a shared terminology is essential to ensure effective communication and understanding among all stakeholders.[4] In the updated guideline, the term "antiepileptic drug" was substituted with "antiseizure medication," in line with ILAE nomenclature.[5] For seizures, epilepsy, and syndromes, the guideline incorporated the classification and concepts outlined in the ILAE position papers published in 2017[17,18] and 2022.[16] However, ILAE terminology was not used consistently, and few older terms such as "West syndrome" (instead of "epileptic spasms syndrome") and "continuous spike-waves in slow sleep" (instead of "epileptic encephalopathy with spike-wave activation in sleep [EE-SWAS]") have been retained.[3] Because the guideline was adopted by the CHMP in February 2025, the refinement in seizure classification introduced in the June 2025 ILAE position paper could not be incorporated.[24]

For add-on studies, an important novelty is the acceptance of the time-to-event (time-to-*n*th seizure) design for confirmatory studies. Advantages of this design include shortening trial duration and minimizing prolonged exposure to placebo or ineffective treatments.[19,25] The latter is a crucial goal given the evidence that patients randomized to placebo in traditional add-on trials showed a sevenfold increase in sudden unexpected death in epilepsy-related mortality compared to those randomized to efficacious ASM doses.[26] A limitation of the time-to-event design is that the size of the control group could be suboptimal for safety assessment because patients randomized to placebo typically exit the trial early. However, recent data suggest that this concern could be unjustified.[27] In any case, the guideline's recommendation that time-to-event should not be the sole design in the clinical development plan is reasonable. This design could be particularly valuable for confirmatory trials in infants and young children with focal seizures[7] or for demonstrating the efficacy in seizure types different from the initially approved indication. The latter approach has been applied successfully to extend approval of lacosamide to the add-on treatment of generalized tonic–clonic seizures.[28]

An important novelty relates to requirements for a monotherapy indication. Concerns about lack of assay sensitivity of the active-control noninferiority design recommended in earlier EMA guidelines have been voiced repeatedly,[20,29] and the feasibility of extrapolating results of add-on trials to the monotherapy setting has been advocated.[30] The EMA's acceptance of the extrapolation approach is a positive development. This alignment with the US Food and Drug Administration, which already accepts extrapolation from add-on data to monotherapy, enhances regulatory consistency across regions. Notably, the EMA guideline specifies that extrapolation is permissible only when certain conditions are fulfilled, which is likely to be the case for many ASMs lacking a monotherapy indication in Europe. Consequently, large double-blind active-controlled noninferiority trials, such as those previously completed in patients with focal seizures,[31–34] are unlikely to be conducted in the future. Some clinicians may find that regrettable, because those trials provided valuable information in a setting close to the routine management of patients with newly diagnosed epilepsy.[35]

The 2025 guideline includes an expanded section for infants and children, with additional recommendations on extrapolating from adults or older children. It provides specific guidance on ASM development in DEEs and other rare epilepsies. For DEEs, researchers will need to refine and specify operational diagnostic criteria for patient selection, building on the initial definitions that have been proposed.[36] The guideline acknowledges that in specific rare DEEs, efficacy may be documented through *n*-of-1 multiple crossover trials.[37] Although the importance of assessing nonseizure outcomes was previously highlighted, this is further emphasized. Reference is also made to disease-modifying studies, although with limited detail, and sponsors are encouraged to seek CHMP advice in this evolving field.[38] Additional points include the

use of video-EEG-based endpoints in children younger than 4 years and the removal of the previous age cutoff of 4 years for extrapolation of focal seizure efficacy, likely reflecting evidence that pathophysiological mechanisms are consistent down to 2 years.[39] This is particularly relevant given the methodological challenges of using video-EEG as a primary endpoint in very young children with focal seizures.[7,40] The use of basket trials (trial designs in which a single investigational product is assessed across multiple epilepsies within a single clinical study) to explore the potential efficacy of investigational ASMs across seizure types and syndromes[41] is still being promoted. However, a recent analysis of pediatric investigation plans showed that this approach has not yet led to the approval of new indications.[42]

The sections on neonatal seizures and SE are especially important, because these areas with high unmet needs were not addressed in previous EMA guidelines. For neonatal seizures, the 2025 guideline incorporates many of the recommendations put forward by the International Neonatal Consortium (INC).[43] The guideline emphasizes that efficacy should preferably be demonstrated through randomized comparative superiority trials. Unlike the INC document, it does not discuss the potential value of Bayesian inference-based or adaptive designs, nor does it provide recommendations on comparator treatments. The use of seizure-free rates over a predefined period as the primary efficacy outcome may be questioned, particularly in neonates with a high seizure burden unresponsive to first-line ASMs, for whom a reduction in seizure burden may be a more realistic endpoint. Future progress in neonatal seizure research should also take into account stratification by acute symptomatic seizures versus neonatal onset epilepsies, as well as by etiology. The requirement of a minimum 30-day follow-up after the last dose is reasonable, and the guideline appropriately highlights the need for longer term, which may be addressed postapproval. Notably, the INC is preparing a complementary paper to integrate recent advances[44] and to reflect the current neonatal seizure treatment guidelines.[45]

The guideline section on the investigation of treatments for SE is relatively brief and provides limited detail. For instance, it does not address the requirements for continuous (video)-EEG assessment in patients with refractory or superrefractory SE. The recommendation to use intravenous (fos)phenytoin or phenobarbital as comparators in second-line treatment trials is debatable, because several recent randomized controlled trials have shown that phenytoin's efficacy and safety are comparable to levetiracetam[46–49] and valproate,[46,47] suggesting that these latter ASMs could serve as equally valid comparators. Moreover, the guideline does not differentiate between pediatric and adult SE, where evidence for ASM efficacy differ. Regarding outcome measures, the use "a functional outcome" as the primary endpoint in refractory SE studies may be problematic, given the challenges of defining validated functional measures in this setting. Including seizure cessation as a coprimary endpoint would therefore appear reasonable.

Overall, the comparison of the 2010 and 2025 EMA guidelines highlights several regulatory advances. The revisions align the EMA guideline with recent scientific progress (including the current ILAE terminology), reduce disparities with US regulatory approaches, address areas that were previously overlooked, and enable more efficient trial designs. Nonetheless, some aspects of clinical trial design and outcome measures still require more precise definition and further refinement. Expanded guidance to support drug development in a broader range of rare epilepsy syndromes would also be welcome, as current indications remain restricted to a few well-characterized syndromes. Guidance would also be welcome on conditions under which approval could be granted for the treatment of a specific seizure type (e.g., focal seizures or generalized tonic–clonic seizures) based on data from studies enrolling patients across different epilepsy syndromes. Likewise, looking ahead, it would be timely for the EMA, in collaboration with experts and patient advocates, to develop specific recommendations for disease-modifying therapies. In particular, there is a need to develop specific guidance for disease-modifying targeted therapies, including small molecules, antisense oligonucleotides, and gene therapies, addressing not only efficacy but also safety considerations, including long-term follow-up and treatment-specific requirements. Similarly, further guidance is warranted on the incorporation and validation of nonseizure outcomes, which are increasingly recognized as essential to capturing the full impact of treatment in epilepsy. In addition, there is a need to develop specific guidance for disease-modifying targeted therapies, including small molecules, antisense oligonucleotides, and gene therapies, addressing not only efficacy but also safety considerations, including long-term follow-up and treatment-specific requirements.

AUTHOR CONTRIBUTIONS

Stéphane Auvin: Design of the study; data collection; analysis of the data; writing the manuscript. **Alexis Arzimanoglou:** Analysis of the data; editing the manuscript. **Jacqueline French:** Analysis of the data; editing the manuscript. **Kelly G. Knupp:** Analysis of the data; editing the manuscript. **Lieven Lagae:** Analysis of the data; editing the manuscript. **Eugen Trinka:** Analysis of the data; editing the manuscript. **Dennis Dlugos:** Analysis of the data; editing the manuscript. **Emilio Perucca:** Design of the study; data collection; analysis of the data; writing the manuscript.

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ACKNOWLEDGMENTS

This report was written by experts selected by the ILAE and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE. Open access publication funding provided by COUPERIN CY26.

CONFLICT OF INTEREST STATEMENT

S.A. is Deputy Editor of *Epilepsia*; has received personal fees for lectures or advice from Angelini, Biocodex, Eisai, Encoded, GRIN Therapeutics, Jazz Pharmaceuticals, Longboard, Lundbeck, Neuraxpharm, Nutricia, Orion, Proveca, Servier, Stoke, UCB Pharma, and Xenon; and has been an investigator for Eisai, Lundbeck, Proveca, Servier, Takeda, and UCB Pharma. A.A. has served on scientific advisory boards for Biocodex, Eisai, Encoded Therapeutics, Jazz Pharmaceuticals, Takeda Pharmaceuticals, UCB, Xenon Pharmaceuticals, Longboard Pharmaceuticals, Lundbeck, Neurvati, and Stoke Therapeutics; has received speaker honoraria from UCB, Biocodex, Eisai, and Jazz Pharmaceuticals; is a Coordinator of the European Reference Network for Rare and Complex Epilepsies, funded by the European Commission; is Codirector of the European Consortium for Epilepsy Trials (ECET); and has received research grants from the European Commission (Horizon and EU4Health programs), UCB, Jazz Pharmaceuticals, Caixa Foundation, and the Spanish Ministry of Health. J.F. receives salary support from the Epilepsy Foundation and from Epilepsy Study Consortium for consulting work and/or attending scientific advisory boards for Acadia Pharmaceuticals, Acuta Capital Partners, Agrithera, Alterity Therapeutics Limited, Angelini Pharma, Autifony Therapeutics Limited, Axonis Therapeutics, Baergic Bio, Beacon Biosignals, Biogen, Biohaven Pharmaceuticals, Bloom Science, Bright Minds Biosciences, Camp4 Therapeutics Corporation, Cerebral Therapeutics, Cerecin, Cerevel, Cognizance Biomarkers, Cowen and Company, Crossject, Eisai, Encoded Therapeutics, Engrail, Epalex, Epitel, Equilibre BioPharmaceuticals, Genentech, GRIN Therapeutics, IQVIA RDS, iQure Pharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Korro Bio, Leal Therapeutics, Lipocine, LivaNova, Longboard Pharmaceuticals, Marinus, Modulight.bio, Neumirna Therapeutics, Neurocrine, Neuronetics, NeuroPace, NeuroPro Therapeutics, Neuroventis, Ono Pharmaceutical Co., Otsuka Pharmaceutical Development, Ovid Therapeutics, Paladin Labs, Praxis, PureTech, Rapport Therapeutics, Receptor Holdings, Sage Therapeutics, SK Life Sciences, Stoke, Supernus, Takeda, Third Rock Ventures, UCB, Ventus Therapeutics, Vida Ventures Management, and Xenon; has also received research support from the Epilepsy Study Consortium (funded by Eisai and UCB,) Epilepsy Study Consortium/ Epilepsy Foundation (funded by UCB), GW/FACES/ One8Foundation; and NINDS; is on the editorial board of *Lancet Neurology* and *Neurology Today*; is Chief Medical/Innovation Officer for the Epilepsy Foundation; is President and on the board of directors for the Epilepsy Study Consortium; and has received travel/meal reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, the Epilepsy Foundation, Angelini Pharma, Biohaven Pharmaceuticals, Cerebral Therapeutics, Cowen and Company, Longboard, Neurelis, Neurocrine, NeuroPace, Praxis, Rapport, SK Life Science, Stoke, Takeda, and Xenon. K.G.K. has

research funding from UCB, Stoke, Eisai, Longboard/Lundbeck, and Encoded; has consulted for UCB, Stoke, Encoded, and the Epilepsy Study Consortium; and is on the data and safety monitoring board for Harmony. L.L. has received speaker honoraria from UCB, Lundbeck, Eisai, Epihunter, and Novartis; is part of advisory boards for UCB and Lundbeck; and holds a patent for the use of fenfluramine in Dravet syndrome and infantile epilepsies. E.T. has received personal honoraria for lectures and educational activities from EVER Pharma, Marinus, Arvelle, Angelini, Alexion, Argenx, Medtronic, Biocodex, Bial-Portela & Ca, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, Epilog, UCB, Biogen, Sanofi, STOKE Therapeutics, Jazz Pharmaceuticals, and Rapport; and is Codirector of ECET. His institution has received research grants from Biogen, UCB Pharma, Eisai, Red Bull, Merck, Bayer, the European Union, FWF Österreichischer Fond zur Wissenschaftsforderung Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. D.D. receives research salary support from the Epilepsy Study Consortium for consulting work and participation on scientific advisory boards/investigator meetings for Acadia, Beacon Biosignals, Biohaven Pharmaceuticals, Bright Minds Bio, Encoded Therapeutics, Epigenyx, GRIN Therapeutics, Jazz Pharmaceuticals, Longboard Pharmaceuticals, Marinus Pharmaceuticals, Praxis, Rapport Therapeutics, SK Life Sciences, Stoke, Stream Neuroscience, Takeda, and UCB; has received travel/meal reimbursement related to research, advisory meetings, or presentation of results at scientific meetings from the Epilepsy Study Consortium, Epilepsy Foundation of America, Lennox Gastaut Foundation, France Foundation, Thomas Jefferson University, and Ministry of Health of the United Arab Emirates. E.P. has received speaker's or consultancy fees from Eisai, GRIN Therapeutics, SK Life Science, Sun Pharma, Takeda, UCB Pharma, and Xenon Pharma and royalties from Wiley and Elsevier. 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at the EMA website at https://www.ema.europa.eu/en/homepage.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Auvin S, Arzimanoglou A, French J, Knupp KG, Lagae L, Trinka E, et al. Evolution of the European Medicines Agency clinical guidelines for epilepsy drug development between 2010 and 2025: A comparative analysis by the ILAE Task Force on Regulatory Affairs. Epilepsia. 2026;00:1–12. https://doi.org/10.1002/epi.70152