Comprehensive Analysis of Epilepsy:
Diagnosis, Epidemiology, and Clinical Trials Insights

NGENŪ CRO

Introduction

Epilepsy is a prevalent neurological disorder characterized by the enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.

This disorder is as old as human history and has been recognized since ancient times. The understanding and treatment of epilepsy has dramatically evolved, influenced by significant advancements in medical science and neurology.

The 19th and 20th centuries saw significant advancements with the introduction of the electroencephalogram (EEG) by Hans Berger, which revolutionized the diagnosis and understanding of epilepsy. In the 21st century, the combination of modern neuroimaging techniques, genetic profiling, and advanced pharmacology has led to an enhanced understanding of epilepsy's complexities, moving away from a one-size-fits-all approach to a more nuanced, individualized treatment strategy.

iNGENŪ CRO

Book a Discovery Call to learn how iNGENū can deliver high-quality, cost-efficient, FDA-compliant research for your next clinical trial

Why Choose iNGENū CRO?

iNGENū is the FDA-centric Australian CRO championing disruptive, innovative biotech firms. We are physician-led, providing access to the full spectrum of clinical and non-clinical research services.

Local Trials, Global Approvals

Australian expertise combined with direct FDA submission capabilities, offering a streamlined path for global approval.

Disciplined, Cost-Efficient Execution

Every dollar is strategically allocated, eliminating unnecessary costs while maintaining the highest quality.

Australian Headquartered, Asia-Pacific Reach

Access high-quality trials in the Asia-Pacific region, enhancing speed and scalability.

Expertise From the Start

Engage directly with our team of highly qualified doctors and PhD scientists from the outset.

Ready to discuss your Clinical Trial?
For further information on how iNGENū can assist you to conduct your clinical trial, book a Discovery Call with one of our Advisors.

Historical Insights on Epilepsy

Key Characteristics of Epilepsy

- **Recurrent Seizures:** The most defining feature of epilepsy is the occurrence of recurrent, unprovoked seizures, which can vary in type, frequency, and severity.
- **Types of Seizures:** Epileptic seizures are broadly categorized into focal (originating in one area of the brain) and generalized (involving both hemispheres of the brain). These categories are further subdivided based on specific characteristics and manifestations.
- **Variability:** The presentation of epilepsy is highly variable, with some individuals experiencing multiple seizures daily while others may have them years apart. The type of seizure, its frequency, and its impact can vary widely among individuals.
- **Neurological Impact:** Beyond seizures, epilepsy can affect various neurological functions, including memory, mood, and cognition, contributing to its complexity and the challenges in management.

Influences

- **Biological Factors:**
  - Genetic Influence
  - Structural Brain Abnormalities
  - Neurotransmitter Imbalance
- **Psychological Factors**
  - Mental Health Correlations
  - Cognitive Effects
  - Social and Emotional Well-being
- **Environmental Factors**
  - External Triggers
  - Medication and Substance Interactions
  - Lifestyle Adaptations

Diagnostic Criteria and Evolving Standards in Epilepsy

ICD-11 Code for Epilepsy

The ICD-11 categorizes epilepsy under the code 8A61. This code encompasses various seizure types and epilepsy syndromes, further classified into more specific categories based on characteristics such as etiology and seizure type. Under the ICD-11, epilepsy is classified with a more nuanced approach compared to previous editions.

Technological Advancements

The introduction and refinement of EEG and neuroimaging techniques have dramatically changed the landscape of epilepsy diagnosis:

- **EEG Technology:** The use of EEG in diagnosing epilepsy has become more sophisticated, allowing clinicians to observe and record the electrical activity of the brain in real-time.
- **Neuroimaging Advances:** MRI and other neuroimaging techniques have provided detailed views of the brain's structure, enabling the identification of structural abnormalities that may cause seizures.

Impact on Research Perspectives

1. **Standardized Definitions and Classifications:** The updated criteria provide a standardized framework for epilepsy research, facilitating consistency across studies.
2. **Focused Research Areas:** By highlighting the importance of genetic, structural, and other etiological factors, the updated criteria guide researchers towards specific areas of inquiry.
3. **Enhanced Study Design:** Clearer diagnostic criteria enable researchers to design studies with well-defined participant groups, improving the reliability and validity of findings.
4. **Data Collection and Analysis:** The emphasis on seizure frequency, treatment response, and EEG findings in the diagnostic process encourages the collection of more detailed data in clinical studies.
5. **Cross-disciplinary Collaboration:** The updates encourage collaboration between neurologists, psychiatrists, neurosurgeons, and other specialists, as well as between clinicians and researchers

Epidemiology of Epilepsy

Global Prevalence and Incidence:
The incidence of epilepsy – the rate at which new cases are diagnosed – varies significantly between countries and regions, influenced by factors such as access to healthcare, diagnostic facilities, and population demographics. Low- and middle-income countries tend to report higher incidence rates, partly due to increased risk factors such as infectious diseases and perinatal complications.

Age-Related Distribution:
There are notable peaks in incidence at different life stages. The condition is most diagnosed in childhood and late adulthood. In children, epilepsy is often associated with genetic factors, congenital abnormalities, and early life insults. In contrast, in older adults, the increased incidence is due to cerebrovascular diseases, brain tumors, and neurodegenerative disorders..

Racial and Ethic Variation:
Epidemiological studies have shown variations in the prevalence and types of epilepsy among different racial and ethnic groups. These differences can be attributed to genetic factors, environmental exposures, and socio-economic status.

Geographical Factors:
Environmental factors, such as exposure to parasites and infectious diseases like cysticercosis, which are more prevalent in certain regions, can increase the risk of developing epilepsy. Additionally, cultural beliefs and stigma associated with epilepsy can vary significantly by location, affecting the likelihood of individuals seeking treatment and receiving an accurate diagnosis.

Genetic Predisposition:
Advances in genetic research have led to the identification of numerous genes associated with epilepsy, shedding light on the complex interplay between genetics and environmental factors. Familial studies and genetic testing are increasingly important for understanding individual risks and tailoring treatment approaches

Socioeconomic Impact:
Epilepsy has a substantial socioeconomic impact, affecting individuals' employment, education, and overall quality of life. The condition can impose a significant financial burden on individuals and healthcare systems, particularly where long-term treatment and care are required.

NGENŪ CRO

FDA-Approved Antiepileptic Drugs: A Closer Look

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Levetiracetam	1999	UCB Pharma	Modulates neurotransmitter release through SV2A binding	Reduces frequency of focal & generalized seizures
Carbamazepine	1968	Novartis	Blocks sodium channels	Effective for focal seizures, secondarily generalized seizures
Lamotrigine	1994	GlaxoSmithKline	Blocks sodium channels, inhibits glutamate release	Broad-spectrum efficacy, particularly in generalized and focal seizures
Valproate	1978	Abbott Laboratories	Increases GABA levels, blocks sodium channels	Broad-spectrum use, effective in generalized seizures, bipolar disorder treatment
Topiramate	1996	Janssen Pharmaceuticals	Blocks sodium channels, enhances GABA activity, inhibits glutamate receptors	Effective in treating generalized and focal seizures, also used for migraine prevention

INGENŪ CRO

Pivotal Endpoints for Epilepsy Clinical Trials

Determining pivotal endpoints in is fraught with challenges that are not only diverse but also deeply intertwined with the heterogeneous nature of epilepsy, the subjective experience of seizures, and the multifaceted outcomes important to patients and clinicians alike. An effective endpoint must encapsulate clinical benefit, address the disease's multifaceted impact, and align with regulatory standards.

Challenges in Determining Endpoints

Inter-Individual Variability:

Patients with epilepsy present a wide range of seizure types, frequencies, and responses to treatment, complicating the establishment of meaningful, uniform endpoints across patient populations.

Defining Seizure Freedom:

Seizure freedom is not achievable for all patients. The definition of "seizure freedom" varies, and for some, a significant reduction rather than complete cessation is a more realistic and meaningful endpoint.

Quantifying Quality of Life:

Epilepsy affects more than just seizure frequency; it impacts quality of life, mental health, and daily functioning. Capturing these effects quantitatively as trial endpoints is challenging but essential.

Measurement & Reporting of Seizures:

Accurate seizure reporting relies heavily on patient or caregiver records, which can be inconsistent. Furthermore, differentiating between seizure types and identifying non-convulsive seizures remains a challenge.

Fluctuating Disease Course:

The natural variability and fluctuating course of epilepsy can confound trial results, as improvements may occur independently of the intervention.

Placebo Responses and Blinding Issues:

The placebo effect is particularly strong in epilepsy trials. Additionally, blinding participants and investigators in trials involving surgical or device interventions is challenging, potentially biasing outcomes.

A Retrospective on Terminated Epilepsy Clinical Trials

Drug Candidate	Clinical Trial Identifier	Reason for termination/drug failure
Perampanel	GDC20003980	Whilst this trial was complete, the endpoint classification of safety and efficacy were not achieved.
Retigabine	NCT01668654	Trial terminated. Endpoints of Pharmacokinetics and Safety partially achieved. The trial was terminated because FDA placed a clinical hold on the pediatric program requiring retigabine discontinuation in subjects, early termination allows for timely reporting of results.
Talampanel	NCT00868361	Trial terminated due to poor recruitment of fast and slow acetylators.
Ganaxolone	NCT02519439	Ganaxolone missed its primary endpoint in the double-blind portion of the 1042-0603(NCT01963208) study. Due to this outcome Marinus Pharmaceuticals discontinued this extension study.
Brivaracetam	NCT00698581	Trial terminated. An interim analysis revealed the study was unlikely to attain a positive outcome for the efficacy analysis. No safety concerns were detected.

Common Failure Points in Epilepsy Clinical Trials

Clinical trials in epilepsy face numerous challenges and failure points that can impact their outcomes and the development of new therapies. Understanding these failure points is crucial for improving trial design, patient outcomes, and the overall success rate of epilepsy research.

Common Failure Points

Inadequate Study Design:

Poorly designed trials, including unclear objectives, inappropriate endpoints, or inadequate sample size, can lead to inconclusive or misleading results. A lack of clear inclusion and exclusion criteria can also affect the study's outcomes.

Patient Recruitment and Retention:

Difficulty in recruiting enough eligible participants or high dropout rates can compromise the statistical power and generalizability of the study. This is often due to stringent criteria, participant burden, or lack of engagement.

Misclassification of Seizure Types:

Incorrectly classifying seizure types or epilepsy syndromes can lead to inappropriate participant grouping, affecting the trial's validity and the applicability of the results to intended populations.

Placebo Effect and Blinding Issues:

A strong placebo effect is common in epilepsy trials, which can obscure the efficacy of the treatment. Maintaining proper blinding can also be challenging, especially in surgical/device-related trials.

Non-Adherence to Treatment Regimens:

Patient non-adherence to the treatment protocol, whether due to side effects, complicated regimens, or lack of understanding, can skew the results and reduce the ability to detect effects.

Variability in Seizure Reporting:

Reliance on patient or caregiver diaries for seizure documentation can introduce bias and inaccuracies due to subjective reporting and recall errors.

Safety Concerns and Standard of Care Treatment Options

Safety Concerns in Epilepsy Management

1. **Medication Side Effects:** Antiepileptic drugs (AEDs) can cause a range of side effects, from mild to severe. Monitoring patients for side effects, adjusting dosages appropriately, and choosing AEDs that best match the patient's profile are crucial steps.
2. **Sudden Unexpected Death in Epilepsy:** SUDEP is a significant concern, though its exact causes are not fully understood. Educating patients and families about SUDEP, promoting seizure control, and discussing lifestyle modifications can mitigate risks.
3. **Status Epilepticus:** This life-threatening condition occurs when seizures last too long or follow one another without recovery. Immediate medical intervention and having an emergency treatment plan are essential for patient safety.
4. **Injury Prevention:** Since seizures can lead to physical injury, this concern directly impacts day-to-day safety for individuals with epilepsy.
5. **Mental Health Risks:** Individuals with epilepsy are more prone to mental health issues, including depression and anxiety. Regular mental health screenings and appropriate interventions should be an integral part of epilepsy care.

Standard Care Practices

1. **Accurate Diagnosis and Classification:** Proper diagnosis, including identifying the type of seizures and the form of epilepsy, is the foundation of effective treatment.
2. **Individualized Treatment Plans:** Selecting the right AED based on seizure type, patient age, comorbidities, and side effects.
3. **Regular Monitoring and Follow-up:** Ongoing assessment of seizure control, medication side effects, and overall health.
4. **Patient Education and Empowerment:** Educating patients and caregivers about epilepsy, treatment options, safety measures, and lifestyle considerations.
5. **Collaborative Care:** A multidisciplinary approach involving neurologists, nurses, pharmacists, psychologists, and social workers ensures comprehensive care.
6. **Addressing Comorbidities:** Identifying and treating comorbid conditions, such as sleep disorders, cardiovascular disease, and bone health issues, is crucial for patients' overall well-being.
7. **Community and Support Services:** Providing access to support groups, educational resources, and community services can help patients and families.

INGENŪ CRO

Enhancing Clinical Trial Protocols: Towards FDA Approval

To enhance the protocol and increase the possibility of FDA approval for an Epilepsy study, it is crucial to integrate the latest scientific insights with regulatory compliance. This involves:

Robust Study Design

Develop a clear, scientifically sound study design with well-defined objectives, endpoints, and inclusion/exclusion criteria. Use adaptive trial designs where appropriate to allow for modifications.

Comprehensive Patient Selection

Ensure a diverse participant pool that accurately reflects the target population. Consider stratification to account for different epilepsy types and severities, improving the applicability of trial findings.

Accurate Endpoint Selection

Choose clinically meaningful endpoints that reflect significant improvements in seizure control, quality of life, or other relevant outcomes. Employ both objective measures and subjective measures.

Rigorous Data Collection & Management

Implement standardized procedures for data collection and handling to ensure accuracy and reliability. Utilize electronic data capture systems and employ regular audits to maintain data integrity.

Minimizing Placebo Effects

Employ strategies such as crossover designs, active comparators, or placebo run-in phases to reduce placebo responses and better isolate the effects of the investigational treatment.

By integrating these strategies, clinical trials for epilepsy can be more effectively designed, conducted, and analyzed, leading to higher quality data and a greater likelihood of FDA approval. Ultimately, these efforts aim to accelerate the development of safe and effective therapies, addressing the unmet needs of patients and advancing the field of epilepsy research and treatment.

Notable Key Opinion Leaders in Epilepsy

Name	Specialty	Designation	Location	Brief Bio
Dr. John-Paul Nicolo, MBBS PhD FRACP	Neurology; Epileptology	Epileptologist	Victoria, Australia	Dr. John-Paul Nicolo is a distinguished epileptologist at The Royal Melbourne Hospital, specializing in the diagnosis and treatment of epilepsy and related neurological conditions. His expertise extends to complex epilepsy management, neuroimaging, and advanced EEG interpretation. Dr. John-Paul Nicolo has been recognized for his contributions to the field of epilepsy, notably through his innovative work in using 7-tesla MRI for identifying brain abnormalities related to epilepsy.
Dr. A Simon Harvey, MBBS FRACP	Neurology	Director	Victoria, Australia	Dr. A. Simon Harvey is the Director of the Children's Epilepsy Program at the Royal Children's Hospital in Melbourne, specializing in pediatric neurology with a particular focus on epilepsy. Dr. Harvey is the clinical lead of the epilepsy program at The Royal Children's Hospital, Melbourne and an honorary research fellow at the Florey Neuroscience Institutes, the Murdoch Children's Research Institute and the University of Melbourne.
Associate Prof. Patrick W Carney, MBBS PhD FRACP	Neurology	Deputy Director	Victoria, Australia	Associate Professor Patrick Carney is the Deputy Director of Neurology at Box Hill Hospital. He completed his undergraduate training at the University of Newcastle and pursued Neurology training in Melbourne at Austin Health and Royal Melbourne Hospital. He holds a PhD in Epilepsy and maintains an active research interest in the field, particularly in imaging and diagnosis following a first seizure. Professor Carney has a significant background in epilepsy, sleep medicine, and general neurology.
Dr. Nicholas D Lawn, MBChB FRACP	Neurology	Neurologist	Western Australia	Dr. Nicholas D. Lawn is a neurologist at Royal Perth Hospital and Sir Charles Gairdner Hospital, known for his innovative use of telehealth to provide patient-centered care. His expertise lies in the areas of epilepsy and EEG, which indicates a strong foundation in diagnosing and treating neurological disorders related to brain activity and seizures.
Associate Prof. Andrew Neal, MBBS PhD FRACP	Neurology	Deputy Director	Victoria, Australia	Associate Professor Andrew is the Director of Epilepsy at Alfred Health and holds clinical appointments at Alfred Hospital, St Vincent's Hospital Melbourne, and Royal Melbourne Hospital. Professor Andrew leads the Stereo-EEG program at Alfred Hospital and cares for a wide range of adult patients with seizures, from those who have had a single episode (that may or may not be a seizure) to those with complex epilepsy. He has a subspecialty interest in managing patients with drug resistant epilepsy being considered for epilepsy surgery and those with brain tumor associated epilepsy.

iNGENū CRO

The Australian CRO championing innovative biotech firms for global success.
Delivering high-quality, FDA-compliant clinical research.

If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com