Executive summary

Epilepsy – which poses a serious burden for patients, with effects on quality of life, work productivity, healthcare needs and risk of premature death – is diagnosed in some 2.4 million people globally each year, and currently affects around 300,000 American children under the age of 14. Pediatric epilepsies present particular challenges, including correct diagnoses, comorbidities and interactions with developmental processes in the brain. While epilepsy is usually controlled with available medication, either as monotherapy or add-on anti-epileptic drug combinations, more than 30% of people with epilepsy do not have adequate seizure control, even with the best available medications. Epilepsy is therefore an active area for R&D, with more than 20 potential therapies in various stages of development. Pediatric trials will be required for many of these products; considerations such as rational study design, careful attention to the specifics of the protocol, and appropriate investigator and site choices are key to successful planning and execution. This paper provides an overview of the 36 industry sponsored, interventional trials involving approximately 6,600 pediatric patients that are currently underway. The authors examine the regulatory and competitive landscape in the United States and Europe. They also describe lessons learned from Quintiles’ experience with 49 epilepsy studies since 2000, recruiting more than 9,300 subjects across 1,200 global sites in 35 countries.
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Introduction

The burden of pediatric epilepsy

The complex spectrum of epilepsy disorders affects some 2.2 million Americans, and is characterized by seizures that differ in type, cause and severity. Globally, some 2.4 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases occur in 30-50 per 100,000 people in the general population. In low- and middle-income countries, this figure can be up to two times higher. Children and older adults are the fastest-growing demographic groups in terms of new cases of epilepsy, and approximately 300,000 American children under the age of 14 have epilepsy. In developed countries, studies indicate that the incidence of epilepsy is high in the first year after birth, and during early childhood, stabilizing after adolescence. Incidence is typically lowest during adulthood through the fifth decade, rising again in the oldest age groups. In developing countries, incidence is high during childhood, with no rise typically seen in older age groups. Epilepsy can occur as a single condition, or co-occur with other conditions that affect the brain, such as cerebral palsy, intellectual disability, autism, Alzheimer’s disease and traumatic brain injury.

The International League Against Epilepsy (ILAE) task force proposed that epilepsy be considered as a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome. At any given time, it is estimated that 50 million individuals worldwide have a diagnosis of epilepsy, with some estimates putting the figure at 65 million or more.

Pediatric epilepsies present broad treatment challenges that are unique to this age group, including the possible diagnoses; the treatment options; the developmental, cognitive and behavioral comorbidities; and the likelihood that these factors interact with developmental processes in the brain.

Unique syndromes in pediatric patients

Significant advances have been made in the diagnosis, evaluation and management of children with epilepsy over the past 15 years. There has been an increase in genetic diagnoses of several key childhood-onset epilepsy syndromes, such as Dravet syndrome, which has been linked to mutations in the SCN1A gene.

Some 20 electroclinical syndromes are recognized by the ILAE, each defined by a distinctive combination of clinical features, signs and symptoms, and electroencephalographic patterns; of these, many begin in childhood. Some of the most common epilepsy syndromes in pediatric patients are benign rolandic epilepsy (BRE), childhood idiopathic occipital epilepsy (CIOE), childhood absence epilepsy (CAE), and juvenile myoclonic epilepsy (JME). Of these, BRE is the most common; this remits by the age of 16, with many children requiring no treatment. For CAE, seizures remit at the rate up to 80%, but JME is viewed as a lifelong condition even if antiepileptic drugs are used. Neonates and infants may also experience seizures that are self-limited, without related psychomotor disturbances, including benign familial neonatal convulsions and benign idiopathic neonatal seizures.

Overlapping indications

Epilepsy often co-occurs with other neurological conditions, according to a study based on data on 731,318 children aged 0 to 11 years from the Norwegian Patient Register. That study found that 6.1% of registered epilepsy patients had autism spectrum disorder (ASD), 7.8% had attention-deficit/hyperactivity disorder (ADHD), and 12.8% had cerebral palsy. Some 11.2% of children with ASD, 5.3% of those with ADHD and 32.5% of those with cerebral palsy also had epilepsy. Other studies suggest that ASD and various forms of epilepsy commonly co-occur, with recent genetic discoveries suggesting a shared biology for both disorders.
In a U.S. study of a nationally representative sample of children, estimated prevalence of reported lifetime epilepsy/seizure disorder was 1%, and of current epilepsy/seizure disorder was 6.3/1000. The study found that developmental, mental health and physical comorbidities were common. Children with seizures were at increased risk for mental health, developmental and physical co-morbidities.

Epilepsy and depression often co-occur in pediatric patients. Treating depression may independently improve both epilepsy and quality of life.

Classification by age
Age of onset is one of many ways in which epilepsy syndromes can be classified. While conceptualizing epilepsies by their underlying etiology is very important, epilepsies may also be classified (based on identified common clinical and EEG characteristics) into epileptic syndromes. Such syndromes have a typical age of seizure onset, a specific seizure presentation, and commonly, typical EEG characteristics. The identification of an epileptic syndrome is useful as it provides information on which underlying etiologies should be considered and which anti-seizure medication(s) might be most useful.

Classification of epileptic seizures
The ILAE classification of seizure types provides the following comprehensive classification of seizure types: partial seizures (simple, complex or evolving to secondarily generalized seizures); seizures that are generalized, myoclonic, clonic, tonic, tonic-clonic (or Grand mal), atonic, or unclassified.

Current therapies
Epilepsy is usually controlled with available medication, either as monotherapy or as add-on anti-epileptic drug (AED) combinations. However, over 30% of people with epilepsy do not have adequate seizure control, even with the best available medications. These patients are then considered to have treatment resistant epilepsy. In cases of intolerance or inefficacy of AEDs, other techniques such as vagal nerve stimulation, deep brain stimulation or surgery are indicated. There is notable off-label use of anti-epileptic medications in certain subtypes of epilepsy, such as the widespread use of clobazam for Dravet Syndrome, despite not having regulatory approval for use in this indication. Regardless of the recognized advances made in the treatment of epilepsy in the past two decades, there is still an unmet need in the overall management of this condition in terms of providing better long-term outcomes and quality of life for patients.

Drugs currently approved for use in adults are often used in children, although this use is often off-label. Those drugs, in many cases, will control simple non-structural seizures; however, many have long-term side effects which are undesirable, especially in a pediatric population. Additionally, seizure syndromes such as Dravet and Lennox Gastaut are treatment resistant to multiple AEDs, and require further development of therapies.

Finally, it is important to note social implications to current therapies that impact compliance and may lead to academic underachievement, and decrease social activities, such as those that expose epileptic patients to increased risk (i.e., swimming). Driving is another complication, with some countries forbidding these patients to drive, which may impact social, school and employment capabilities. Multiple AEDs have noted cosmetic effects such as non-negligible weight gain, hair loss, gingival hypertrophy and acne, just to name the most common ones. A key consideration when prescribing AEDs to young female patients, is the drug interaction with oral contraception, and the potential effect on the unborn baby (birth defects) in pregnant epileptic women.

R&D pipeline
As of March 2016, there are 36 industry sponsored, interventional trials involving approximately 6,600 pediatric patients with various forms of epilepsy globally. The distribution of these trials by reported phase of development is shown in Figure 1. This is inclusive of trials not yet actively recruiting patients as well as those that are recruiting both pediatric and adult patients. Of these 36 trials, 17 are recruiting pediatric patients exclusively. The ages of the target population are derived from any combination of the epidemiology of the specific epilepsy type under study, regulatory commitments, or scientific needs of the individual study.
A summary of the epilepsy types under evaluation in these active trials is shown in Figure 2.

As there continues to be a need for more effective treatments for epilepsy, especially for treatment resistant forms, that have fewer side effects, the development landscape for these indications is expected to grow in the coming years.
The regulatory landscape

Overview of pediatric regulations

As the result of pediatric regulations in the United States and Europe, most therapies being developed to treat epilepsy will be required to be studied in pediatric populations. A summary of the regulations is provided in Table 1. Waivers will be granted only if specific criteria are met:

• The drug is not expected to be safe or efficacious in children

• The disease occurs only in adults (EU) or studies are impossible/highly impracticable, e.g., because the number of patients is so small (U.S.), or

• No significant benefit over existing therapies is anticipated.

In the U.S., to use the “no significant benefit” criteria, it is also necessary to demonstrate that the drug is not likely to be used in a substantial number of pediatric patients.

Deferrals of pediatric studies, often until after approval of the drug for adult use, are granted in several circumstances:

• When it is appropriate to conduct studies in adults first

• When studies in children will take longer, or

• When additional time is needed to develop pediatric formulations.

Deferrals enable initial evidence of positive benefit: risk to be collected in adults prior to conducting trials in children, and also avoid delaying the approval of the drug for adults. While completion of pediatric studies is generally not done prior to initial approval of the drug (unless the specific indication occurs predominantly in children), regulatory authorities may request initiation of the studies prior to approval, and an approved pediatric development plan must be in place before the New Drug Application/Biologics License Application (NDA/BLA) can be approved or the Marketing Authorization Application (MAA) can be submitted.

In the EU, the Paediatric Regulation provides both the mandate for pediatric studies and the incentive of an additional six months of marketing exclusivity. In the U.S., the Pediatric Research Equity Act (PREA) provides the authority to require pediatric studies, and the Best Pharmaceuticals for Children Act (BPCA) provides the six-month additional marketing exclusivity incentive. Both of these Acts were made permanent in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), which also introduced the requirement for a Pediatric Study Plan (PSP) that must be submitted within 60 days of the End of Phase 2 meeting. In Europe, a Pediatric Investigational Plan (PIP) is to be submitted after completion of pharmacokinetic (PK) studies in adults.

Likely the most important advice that can be given to a biopharma company is to prepare a pediatric plan early in development, keeping in mind that creation and execution of the plan may have very different timelines. A pediatric development program typically will be multi-phase, proceeding from studies in adults on bioavailability of pediatric formulations, when needed, to PK studies, and then efficacy and long-term safety studies. By having a well-developed plan in place early in development, pediatric requirements need not delay market entry of a drug.

Regardless of the recognized advances made in the treatment of epilepsy in the past two decades, there is still an unmet need in the overall management of this condition in terms of providing better long-term outcomes and quality of life for patients.
Table 1: U.S. and EU pediatric regulations: Similarities and differences

<table>
<thead>
<tr>
<th></th>
<th>U.S.</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission</td>
<td>Pediatric Study Plan (PSP)</td>
<td>Pediatric Investigation Plan (PIP)</td>
</tr>
<tr>
<td>Definition of pediatric</td>
<td>Through 16 years old, inclusive</td>
<td>Through 17 years old, inclusive</td>
</tr>
<tr>
<td>Scope</td>
<td>New indication</td>
<td>Prior and new indications</td>
</tr>
<tr>
<td></td>
<td>Additional indications can be required for exclusivity</td>
<td></td>
</tr>
<tr>
<td>Waiver</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Deferral</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reward</td>
<td>6 month pediatric exclusivity if BPCA (Best Pharmaceuticals for Children Act, 2002) Written Request issued and fulfilled for the study</td>
<td>6 month Supplementary Protection Certificate</td>
</tr>
<tr>
<td>Submission timing</td>
<td>Within 60 days of the end-of-phase 2 (EOP2) meeting</td>
<td>After the completion of adult PK</td>
</tr>
<tr>
<td>Approval timing</td>
<td>Required prior to NDA/BLA approval</td>
<td>Required prior to MAA submission</td>
</tr>
<tr>
<td>Orphan drugs</td>
<td>Exempt from pediatric requirements</td>
<td>Not exempt, but eligible for additional 2 years exclusivity</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>Not exempt from pediatric requirements</td>
<td>Exempt from pediatric requirements</td>
</tr>
</tbody>
</table>

Return on investment for the sponsor
Even with the substantial investment that can be associated with fulfillment of pediatric regulatory requirements, the return on investment is generally positive due to extension of marketing exclusivity.\textsuperscript{25,26} While both the U.S. and EU offer six-month extensions of exclusivity, in the U.S., exclusivity is granted only if the studies are the subject of an FDA Written Request per the BPCA, which necessitates a process that is separate from the approval of the PSP. Whereas the studies that can be required under the PREA are limited to the new indication being sought in adults, Written Requests can encompass additional indications, including those previously approved and/or those not in the label, if the FDA believes this information will improve use of the drug in children. In the EU, the granting of exclusivity is more directly linked to the PIP process, and all indications in the label, both those previously approved and the new indication, are expected to be addressed in the PIP. In the EU, there is also a special marketing application for off-patent drugs developed for pediatric use called the Pediatric Use Marketing Application (PUMA) that results in 10 years of exclusivity.

Regulatory considerations specific to pediatric epilepsy therapies
Over the past 15 years, regulatory authorities have recognized the need for early assessment of efficacy of AEDs to treat pediatric epilepsy, with the result that increasing numbers of AEDs have become available for the treatment of a younger population.\textsuperscript{27} While some were initially licensed for adults and subsequently for children (e.g., levetiracetam and topiramate), an increasing number have been licensed for children from the outset (e.g., rufinamide and perampanel).\textsuperscript{28} Drugs to treat indications that predominantly affect children or have an onset in childhood, such as Dravet or Lennox-Gastaut syndromes, typically include children early in the clinical program, after Phase 1 safety studies in healthy adult volunteers.

Orphan designation has been granted to numerous pediatric epilepsy therapies. Several orphan designated products are currently in development, and others have attained approval for the orphan indication. Orphan designation provides multiple incentives for product development including tax credits for clinical research, reduced regulatory fees and potentially greater flexibility in the clinical development program. One of the greatest incentives is the granting of additional marketing exclusivity for the orphan indication at the time of product approval, seven years in the U.S. and 10 years in the EU.

The most important advice that can be given to a biopharma company is to prepare a pediatric plan early in development, keeping in mind that creation and execution of the plan may have very different timelines.

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Footnotes:
\textsuperscript{25} BPCA: Best Pharmaceuticals for Children Act, 2002
\textsuperscript{26} PREA: Pediatric Research Equity Act
\textsuperscript{27} Dravet: Dravet Syndrome
\textsuperscript{28} Lennox-Gastaut: Lennox-Gastaut Syndrome
Orphan drug regulations were adopted more recently in the EU than in the U.S. (2000 vs. 1983), and EU regulations have an additional requirement that there be no satisfactory authorized treatment (or that the to-be-designated product offers significant benefit), both of which likely contribute to the smaller number of orphan drug designations for pediatric epilepsy therapies in the EU compared to the U.S. In the U.S., seven therapies have received orphan designation for infantile spasms, with vigabatrin and repository corticotrophin or adrenocorticotropic hormone being approved for that use. Eight sponsors have received U.S. orphan drug designation for seven drugs for the indication of Lennox-Gastaut, five of which are now approved for the indication (lamotrigine, topiramate, felbamate, clobazam and rufinamide). Four sponsors have received U.S. orphan drug designation for three drugs for the indication of Dravet syndrome, but none has yet been approved for the indication. Stiripentol, one of the drugs with U.S. and EU orphan designation for Dravet syndrome, has been approved in Europe, Canada and Japan.

Considerations for successful pediatric clinical trials in epilepsy

Several considerations are of particular importance for the successful planning and execution of pediatric clinical trials. These are discussed individually, and include:

- Rational study design
- Careful attention to specifics of the protocol as they pertain to pediatric participants
- Technological advancements that ease the burden of study participation
- Principal Investigator (PI) and investigational site characteristics, including PI involvement
- Recruitment and retention of participants and their families
- Operational considerations, including country and site selection.

Rational study design

Pediatric protocol development is not merely a process of changing the age ranges employed in a similar adult trial, but requires thoughtful consideration with regard to pediatric-specific issues. Designing a protocol for a pediatric clinical trial requires an understanding of developmental physiology, emotional development, and the particular clinical and pathologic manifestations of the disease being studied. Often, while the particular disease process is similar between adults and pediatric patients, it is not identical. As such, specific endpoints applicable to adults may not be applicable to children.

When recruiting for adult clinical trials, participants must have the disease or condition of clinical concern, but there may be a fair degree of latitude with regard to age, as most outcome assessments will be applicable across age groups. However, in pediatric clinical trials, different pediatric age groups may require different assents, modification of endpoint definitions, and use of age-appropriate laboratory norms. To develop an acceptable and effective pediatric epilepsy protocol, these age-specific factors must be addressed.

Attention to protocol specifics

Specific protocol elements may also require a special approach when tailoring the design to include pediatric patients. These include requirements for specialized diagnostic procedures, which must be appropriate for children, anticipation of family needs if an overnight stay is required (such as for video EEG), and specific requirements for pharmacokinetic (PK) sampling. Restrictions exist on the volume of blood drawn, which impacts the number and timing of PK and/or lab samples. If such samples are to be taken, age-specific blood volumes must be considered. It is generally accepted that 3% of estimated circulating blood volume can be removed for study purposes over a two to eight-week period, but requirements are often governed by individual Institutional Review Boards (IRBs) and/or Ethics Committees.
Independent of the blood volume differences, various developmental factors influence PK sample timing and analysis. These factors include expanded volume of distribution, which is maximal in infancy and decreases to adult ranges during late adolescence, and increased renal excretion, which changes with pediatric renal function across the age spectrum. Breastfeeding versus formula feeding in newborns and infants is also relevant as this impacts gastric emptying time.

In general, most applicable pediatric programs should include the following:

- Informed consent and assent
- Ethical considerations, including 21 Code of Federal Regulations (CFR) Part 50 definitions of risk
- Safeguards for patient safety and monitoring, including rescue plans if appropriate
- Good rationale for a placebo challenge or placebo arm if one is used, and
- Therapeutically specific, age-appropriate endpoints.

**Technology advancements**

Technology and the ease of communication it provides can ease the burden for sites and families enrolled on a clinical trial. Technology is often well-accepted by children at a very young age, facilitating the use of electronic data capturing. For pediatric epilepsy trials, useful technological advancements may include:

- eConsent platform, helping to mitigate issues when dual parent consent is required and both parents are not available to attend study visits; and providing interactive materials to support the consent and assent process.
- Investigator portal, housing relevant study materials, including current protocols, approved ICF/Assents, recruitment and retention materials, FAQ logs, etc.
- eDiary/ePRO, facilitating patient and caregiver reporting in an accessible platform
- Activity tracking, via smart phones and other personal devices that can track activity, sleep habits, and even quality of breath, thus replacing some components of diaries with more objective measures.
- Seizure documentation, with portable video devices allowing for documentation of seizure activity; however, video EEG within a controlled, hospital setting is a standard for many pediatric epilepsy trials.

**Principal Investigator and site characteristics**

Ideal Principal Investigators (PIs) for pediatric epilepsy studies include: neurologists, pediatric neurologists, epileptologists, pediatricians, primary care physicians, and specialists at epilepsy centers, neurology clinics with neurologists with a subspecialty in epilepsy, and university centers. In some settings, adult neurologists may manage pediatric epilepsy patients, especially in older adolescents. Ideal sites offer a large pool of available subjects with different types of epilepsies and epileptic syndromes, encompassing a spectrum of severities of the condition. The referral base can include community neurologists and pediatricians, primary care physicians and internal medicine specialists.

Sites that are most suitable include those with a PI and staff who have research experience in pediatric epilepsy. Urban locations are typically preferred, but non-urban settings can also be suitable, depending on accessibility and size of target population. Care must also be taken to consider the referral base for the clinical investigation site. In the case of complex or intractable epilepsies, specialized referral centers may have large catchment areas, while in developing countries, there may be relatively few referral centers available. As patients and families may travel a considerable distance to sites for routine clinical care and clinical trial participation, understanding and facilitating the accessibility of the site to patients is often paramount to the success of pediatric epilepsy clinical trials.

In pediatric trials, it is the family that is “enrolled,” and not just the patient. The sites therefore need to be both patient- and family-friendly.
Locating trial participants
An overview of a process for outreach, screening, referral and tracking appears below (Figure 3):

Figure 3: A process for recruiting clinical trial participants

Online communities are a promising way to identify, gain insights and recruit clinical trial participants, including:

- **MediGuard.org**, a medication monitoring service designed to connect with a large number of patients for potential research opportunities. Currently, over 2.6 million patients in the U.S., UK, France, Germany, Spain and Australia have registered for MediGuard’s service, with over 99% expressing interest in research opportunities. This makes MediGuard.org one of the largest and fastest growing healthcare communities in history.

- **ClinicalResearch.com**, created by Quintiles to increase awareness of, understanding of, and participation in clinical trials. Since its inception, ClinicalResearch.com has built research-friendly relationships, matching more than 50,000 patients to clinical trial opportunities.

In addition to the online communities, it is advantageous to contact patient based epilepsy networks to share information about a clinical trial, assist with identifying sites, patients and/or key opinion leaders within a specific indication, and to evaluate feasibility and endpoint determination of a study. Examples of these networks include:

- **Epilepsy Foundation** – a community-based, family-led organization dedicated to improving the lives of all people impacted by seizures with local family and patient support groups as well as online support.

- **Local epilepsy support groups** – regionally available and often affiliated with larger academic centers that serve epileptic populations.

**Patient retention**
Patient recruitment is a challenge in pediatric clinical trials, but generally, recruitment into epilepsy trials is manageable as the caregivers are heavily involved in the trial decisions. Thus, when discussing epilepsy trial recruitment and retention, it is critical to include the caregiver as playing a pivotal role in the patient’s participation. Successful strategies for patient retention in epilepsy trials include:

- Caregiver support groups
- Providing meals on-site for patients and their families so that they do not have to go to the hospital cafeteria or off-site for meals
- Taxi/car park passes, valet for hospital visits, or travel concierge services
- Pleasant clinics for patients and families offering a time of respite for the caregiver while the patient is under site management
- Priority scheduling at flexible times to alleviate missed work or school
- Loyalty and appreciation cards
- Visit reminders.
Operational considerations – site selection
In epilepsy clinical trials, it is increasingly common to rely on less developed regions for time- and cost-efficiencies. Differences in baseline medical practice must be taken into account in these regions, including the availability of AEDs and other treatments, characteristics of patient/physician relationships, safety reporting, the potential for reduced signal/noise ratio and specifically, the placebo response rate. In addition, screen failure rates may be high, particularly if the clinical trial protocol requires completion of a seizure diary during the screening period. Seizure diaries can be particularly challenging in the pediatric population, where there can be multiple seizure types and multiple caregivers assisting with diary completion. Careful consideration of how the diary will be completed and training of study staff and the caregiver(s) or child will be necessary.

Competitive landscape
As with many other pediatric indications, the competitive research landscape also influences the operational feasibility of clinical trials. In pediatric epilepsy, multiple actively enrolling trials conducted at a finite number of pediatric epilepsy research sites can adversely affect the availability of patient and investigator resources at clinical trial sites. Although the 36 ongoing studies in this space may not seem high, the impact may be notable given the limited number of qualified investigators available and the relatively small number of eligible patients at any one site. Furthermore, the presence of multiple developers pursuing products treating similar epilepsy subtypes, especially those that are infrequently seen, increases competition dramatically. Such competitive pressures present unique challenges to drug developers, investigator sites and CROs who must balance the clinical necessity of developing safe and effective treatments for children with epilepsy with the existing research landscape to enable successful evaluation of these treatments.

Lessons learned based on Quintiles’ experience in adult and pediatric epilepsy
Quintiles has carried out 49 epilepsy disease studies since 2000, which have recruited in excess of 9,300 subjects across 1,200 global sites in 35 countries. Of these, 12 studies assessed pediatric population as per Figure 4.

Figure 4: Patients recruited into epilepsy trials (January 2000 to July 2015)
The company’s operational experience in epilepsy spans nearly all regions of the world and includes patients in all stages of the disease (Figure 5).

**Figure 5: Total epilepsy patients recruited by subindication**

![Pie chart showing distribution of epilepsy patients by subindication]

- Epilepsy – Newly diagnosed
- Epilepsy – Unspecified
- Partial onset seizures
- Pediatric – Lennox-Gastaut Syndrome
- Pediatric – Partial onset seizures
- Pediatric – Unspecified
- Refractory – Acute repetitive seizures
- Refractory – Partial onset seizures
- Refractory – Unspecified

**Conclusions**

Epilepsy represents a serious burden for patients, with significant implications for quality of life, work productivity, healthcare needs and risk of premature death. As well as occurring singly, epilepsy may be comorbid with other conditions affecting the brain, such as cerebral palsy, intellectual disability, autism, Alzheimer’s disease and traumatic brain injury. Pediatric epilepsies present treatment challenges unique to this age group, including correct diagnoses, comorbidities and interactions with developmental processes in the brain. This population is in critical need of optimized, effective therapy.

Promising improvements have been made in the diagnosis, evaluation and management of children with epilepsy over the past 15 years. However, while epilepsy is often controlled with available medication, side effects remain a problem. In addition, over 30% of people with epilepsy do not have adequate seizure control. Both areas represent major unmet needs in the overall management of this condition. The ideal therapy would be one that completely stops seizure occurrence, with no or very few side effects, an easy dosing schedule, minimal drug interactions, and the ability to reduce injuries and accidental death due to seizures, while maximizing quality of life.

Epilepsy remains an active area for R&D, with over 20 potential therapies in various stages of development. Pediatric trials will have to be completed for many of these therapies and considerations such as rational study design, careful attention to the specifics of the protocol, as well as appropriate investigator and site choices are key to successful planning and execution of pediatric trials in this challenging space.

The ideal therapy would be one that completely stops seizure occurrence, with no or very few side effects, an easy dosing schedule, minimal drug interactions, and the ability to reduce injuries and accidental death due to seizures, while maximizing quality of life.
Acknowledgments

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References


References


References


32. Quintiles has developed an internal, proprietary database using illustrative, de-identified data from many sources. These data are referenced throughout the text.
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Marie Trad
Executive Medical Director, Drug Development, Neurology Center of Excellence, Quintiles

Dr. Trad has over 26 years of CNS experience, of which 11 years as a clinical neurologist/neuroradiologist and 15 years of pharmaceutical industry experience as a clinical research specialist/consultant. Her 15 years of drug development experience focused on the CNS area. Experience in clinical trial management providing medical, clinical and global strategic support related to neurology and psychiatry trials in the following specialized areas: epilepsy (both monotherapy and add-on therapy), idiopathic Parkinson’s disease (Early and Advanced IPD), Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), post-herpetic neuralgia (PHN), chronic and acute pain, migraine, traumatic brain injury (TBI), attention deficit-hyperactivity disorder (ADHD), sleep disorder (narcolepsy), stroke, bipolar disorder, generalized anxiety disorder (GAD), social phobia, major depressive disorder (MDD), schizophrenia. Significant experience in neuroradiology: MRI, MRA and CT-scan of head, neck and spine.

Cathy Vanbelle, RN
Director, Deputy, Neurology Center of Excellence, Quintiles

Cathy Vanbelle has 23 years’ experience in conducting and supporting clinical trials and currently serves as Director within the Neurology COE group, where she supports internal and external customers with delivery metrics and analysis of all kinds. She joined Quintiles in 1998 as a clinical research manager, where after she joined the regional analytics group. She set up the global feasibility group and spent five years before moving to the Central Nervous System therapeutic team in 2008. Cathy has solid experience in global strategic study implementation over all therapeutic areas. As a registered pediatric nurse and with her degree in oncology, she has worked for 10 years on a pediatric bone marrow transplantation ward.