

## **Evidence-Based Practice Center Systematic Review Protocol**

### **Project Title: Evaluation of Effectiveness and Safety of Antiepileptic Medications in Patients With Epilepsy**

#### **I. Background and Objectives for the Systematic Review**

##### **Incidence and Prevalence of Epilepsy**

Seizures are single or paroxysmal events arising from abnormal, excessive, hypersynchronous discharges from central nervous system neurons and range in severity from symptoms not readily apparent to an observer to dramatic convulsions.<sup>1</sup> Epilepsy describes a clinical phenomenon in which a person has recurrent seizures due to a chronic, underlying process.<sup>1,2</sup>

Over a lifetime, approximately 10 percent of people in the United States will suffer a seizure with 1 percent to 3 percent developing epilepsy.<sup>2-4</sup> The annual incidence of epilepsy is about 50 per 100,000 with a prevalence of 5-10 per 1000.<sup>4,5</sup>

##### **Classifying a Seizure and an Epilepsy Syndrome**

Antiepileptic drug therapy is the mainstay of treatment for most patients with epilepsy. Seizure classification is an important element in designing the treatment plan, since some antiepileptic drugs have different activities against various seizure types. The International League Against Epilepsy classify the three main types of seizures: partial, generalized, and unclassified. The main subtypes are given in Table 1.<sup>1</sup> Partial seizure activity is restricted, at least initially, to discrete areas of the cerebral cortex while generalized seizure activity occurs in diffuse regions of the brain simultaneously. If consciousness is fully preserved during the partial seizure, it is termed a simple partial seizure. If consciousness is impaired during the partial seizure, it is termed a complex partial seizure. If a seizure begins as a partial seizure and then spreads diffusely throughout the cortex, it is termed a partial seizure with secondary generalization. Because of the focused nature of a partial seizure, only a specific area of the body is usually involved, at least initially. Generalized seizures are termed absence seizures if they are characterized by sudden, brief lapses of consciousness without loss of postural control. Absence seizures usually begin in childhood (ages 4-8) or early adolescence and are the main seizure type in 15-20 percent of children with epilepsy. Generalized seizures are termed generalized tonic-clonic seizures if they are characterized by generalized muscle contraction for a period followed by intermittent muscle contraction and relaxation. There is usually a postictal phase with confusion that accompanies the end of convulsions. Generalized seizures are the main seizure type in approximately 10 percent of people with epilepsy. Generalized seizures are termed atonic seizures if sudden loss and then regaining of postural muscle tone characterize them. While consciousness is briefly impaired, there is usually no postictal confusion in people with atonic

seizures. Generalized seizures are termed myoclonus seizures if a sudden jerking movement of the skeletal muscle characterizes it. A patient with epilepsy may experience more than one subtype of seizure over their lifetime.<sup>1</sup>

Epilepsy syndromes are disorders in which epilepsy is a predominant feature and there is sufficient evidence suggest a common underlying mechanism.<sup>1</sup> Three main epilepsy syndromes have been classified, one associated with partial seizures (Mesial Temporal Lobe Epilepsy syndrome) and the other associated with generalized seizures (Juvenile Myoclonic Epilepsy syndrome and Lennox-Gastaut Epilepsy syndrome). Mesial Temporal Lobe Epilepsy syndrome is associated with complex partial epilepsy and has distinctive clinical, electroencephalographic, and pathologic findings. High-resolution MRI can detect the characteristic hippocampal sclerosis that appears to be essential in the pathophysiology of the syndrome. Epilepsy in people with this syndrome tends to be refractory to treatment with anticonvulsants but responds well to surgical intervention. Juvenile Myoclonic Epilepsy syndrome is a generalized seizure disorder that appears in early adolescence. While most of the seizures the patient experiences consist of bilateral myoclonic jerks; people may also experience tonic-clonic or absence seizures. The condition is otherwise benign, and although complete remission is uncommon, the seizures respond well to anticonvulsant medication. Lennox-Gastaut Epilepsy syndrome occurs in children and is defined by the following triad: multiple seizure types (generalized tonic-clonic, atonic, and atypical absence), specific electroencephalographic findings (<3 Hz spike-and-wave discharges), and impaired cognitive function. Lennox-Gastaut Epilepsy syndrome is associated with central nervous system delays or dysfunction from a variety of causes, including developmental abnormalities, perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions. The multifactorial nature of this syndrome suggests that it is a nonspecific response of the brain to diffuse neural injury. Unfortunately, many patients have a poor prognosis due to the underlying central nervous system pathology and the consequences of severe, poorly controlled epilepsy.<sup>1</sup>

**Table 1. Classification of seizure types<sup>1</sup>**

Seizure Type	Subtypes
Partial Seizures	Simple partial seizures Complex partial seizures Partial seizures with secondary generalization
Generalized Seizures	Absence Tonic-clonic Tonic Atonic Myoclonic
Unclassified Seizures	Neonatal seizures Infantile spasms

## Age and Epilepsy

The incidence of new-onset epilepsy is high during the first nine years of life and then plateaus over the next 30 years.<sup>1</sup> The incidence of new onset epilepsy drops in 40-59 year olds, and then rises again in the elderly.<sup>4,5</sup> The age of epilepsy onset is marked by different underlying causes as depicted in Table 2.<sup>1,2,5</sup> Childhood marks the age at which many of the well-defined epilepsy syndromes become present. During adolescence and early adulthood, there is a

transition away from idiopathic or genetically-based epilepsy to more cases secondary to acquired central nervous system lesions (head trauma, infections, and brain tumors). A patient with a penetrating head wound, depressed skull fracture, intracranial hemorrhage, or prolonged posttraumatic coma or amnesia has a 40-50 percent risk of developing epilepsy, while a patient with a closed head injury and cerebral contusion has a 5-25 percent risk. The causes of seizures in older adults include cerebrovascular disease, trauma (blunt trauma and subdural hematoma), brain tumors, and degenerative diseases such as Alzheimer's disease. Cerebrovascular disease may account for approximately 50 percent of new cases of epilepsy in patients older than 65 years.<sup>1</sup>

**Table 2. Epilepsy etiology based on age<sup>1,2,5</sup>**

Age Group	Epilepsy Causes
Children	Genetic disorders Developmental disorders Central nervous system infection Trauma Idiopathic
Adolescents/Young Adults	Trauma Genetic disorders Infection Brain Tumor Idiopathic
Older Adults	Trauma Cerebrovascular accidents Brain tumor Degenerative diseases (Alzheimer's disease) Idiopathic

## Antiepileptic Medications

The overall goal of antiepileptic therapy is to prevent seizures and avoid untoward side effects with a regimen that is convenient and easy to follow. People with epilepsy usually initiate treatment with one antiepileptic drug at the time of diagnosis, but 30 percent of patients will be refractory to this medication.<sup>6</sup> While control of seizures is the overriding goal of therapy, selecting an effective drug with the least potential for side effects becomes a crucial decision for clinicians. In addition to traditional adverse effects, fertility is also an issue with some agents causing teratogenicity and CYP enzyme inducers reducing the effectiveness of oral contraceptives.

Table 3 identifies approved medications for the treatment of epilepsy, their known or suspected mechanism of action, type of seizures principally treated, adverse effects, drug interaction potential, and availability of a generic product.<sup>1,2,7-9</sup>

**Table 3. Important characteristics of antiepileptic medications<sup>1,2,7-9</sup>**

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Carbamazepine	Na <sup>+</sup> channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, vertigo Non-Neurological: aplastic anemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash*	Enzyme Substrate: CYP 3A4, 2C8 Enzyme Inducer: CYP 1A2, 2B6, 2C8, 2C9, 2C19, 3A4 Enzyme Inhibitor: None	Yes
Clonazepam	Potentiate GABA receptor function	Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, lethargy Non-Neurological: anorexia	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Ethosuximide	T-type Ca <sup>2+</sup> channel inhibition in thalamus	Absence	Neurological: ataxia, lethargy, headache Non-Neurological: gastrointestinal irritation, skin rash, bone marrow suppression	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes, Only Available in Generic
Felbamate	NMDA receptor antagonist and increase GABA availability	Partial Lennox-Gastaut	Neurological: insomnia, dizziness, sedation, headache Non-Neurological: aplastic anemia, hepatic failure, weight loss, gastrointestinal irritation	Enzyme Substrate: CYP 2E1, 3A4 Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	No, but Patent Expired 9/26/09
Gabapentin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: sedation, dizziness, ataxia, fatigue Non-Neurological: gastrointestinal irritation, weight gain, edema	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	Yes
Lacosamide	Na <sup>+</sup> channel inhibition	Partial	Neurological: headache, dizziness, diplopia, ataxia, fatigue, tremor, somnolence, blurred vision Non-Neurological: Nausea, vomiting, diarrhea	Enzyme Substrate: CYP 2C19 Enzyme inducer: None Enzyme Inhibitor: CYP 2C19	No

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Lamotrigine	Decrease glutamate release	Partial Tonic-Clonic Atypical Absence Myoclonic Lennox-Gastaut	Neurological: dizziness, diplopia, sedation, ataxia, headache Non-Neurological: skin rash*	Enzyme Substrate: UGT1A4 Enzyme inducer: None Enzyme Inhibitor: None	Yes
Levetiracetam	Synaptic vesicle release modulation	Partial	Neurological: sedation, fatigue, incoordination, psychosis Non-Neurological: anemia, leucopenia	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	Yes
Oxcarbazepine	Na <sup>+</sup> channel inhibition	Partial	Neurological: fatigue, ataxia, dizziness, diplopia Non-Neurological: aplastic anemia, leucopenia, gastrointestinal irritation, hepatotoxicity, hyponatremia, skin rash	Enzyme Substrate: CYP Enzyme Inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes
Phenobarbital	Potentiate GABA receptor function	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-Neurological: Skin rash, hepatotoxicity	Enzyme Substrate: CYP 2C9, 2C19, 2E1 Enzyme Inducer: CYP 1A2, 2A6, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes, Only Available in Generic
Phenytoin	Na <sup>+</sup> and Ca <sup>2+</sup> channel inhibition	Partial Tonic-Clonic	Neurological: dizziness, diplopia, ataxia, confusion Non-Neurological: gingival hyperplasia, peripheral neuropathy, lymphadenopathy, hirsutism, osteomalacia, hepatotoxicity, facial coarsening, skin rash*	Enzyme Substrate: CYP 2C9, 2C19, 3A4 Enzyme Inducer: CYP 2B6, 2C8, 2C9, 2C19, 3A4 and UDPGT Enzyme Inhibitor: None	Yes

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Pregabalin	GABA analogue for alpha-2 delta subunit	Partial	Neurological: ataxia, somnolence, dizziness, blurred vision, diplopia Non-Neurological: peripheral edema, increased appetite	Enzyme Substrate: None Enzyme Inducer: None Enzyme Inhibitor: None	No
Primidone	Inhibition of neuronal firing	Partial Tonic-Clonic	Neurological: sedation, ataxia, confusion, dizziness, decreased libido, depression Non-Neurological: Skin rash	Enzyme Substrate: None Enzyme inducer: CYP 1A2, 2B6, 2C8, 2C9, 3A4 Enzyme Inhibitor: None	Yes
Rufinamide	Na <sup>+</sup> channel inhibition	Lennox-Gastaut	Neurological: headache, dizziness, fatigue, somnolence, convulsion, diplopia, tremor, nystagmus Non-Neurological: nausea, vomiting, nasopharyngitis, blurred vision	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Tiagabine	Increase GABA availability	Partial Tonic-Clonic	Neurological: confusion, sedation, depression, speech problems, paresthesias, psychosis Non-Neurological: gastrointestinal irritation	Enzyme Substrate: CYP 3A4 Enzyme inducer: None Enzyme Inhibitor: None	No
Topiramate	Na <sup>+</sup> channel inhibition	Partial Tonic-Clonic Lennox-Gastaut	Neurological: psychomotor slowing, sedation, speech problems, fatigue, paresthesias Non-Neurological: kidney stones, glaucoma, weight loss, hypohydrosis	Enzyme Substrate: None Enzyme inducer: CYP 3A4 Enzyme Inhibitor: CYP 2C19	Yes

Drug Name	Mechanism of Action	Seizure Types Treated	Adverse Effects	Drug Interactions	Generic Available
Valproic Acid	T-type Ca <sup>++</sup> channel inhibition in thalamus increase GABA availability	Partial Tonic-Clonic Absence Atypical Absence Myoclonic	Neurological: ataxia, sedation, tremor Non-Neurological: Hepatotoxicity, thrombocytopenia, gastrointestinal irritation, weight gain, hyperammonemia	Enzyme Substrate: UGT 1A6, 1A9, 2B7, beta-oxidation Enzyme Inducer: CYP 2A6 Enzyme Inhibitor: CYP 2C9, 2C19, 2D6, 3A4	Yes
Vigabatrin	Analog of GABA, inhibits GABA catabolism	Complex Partial	Neurological: headache, fatigue, drowsiness, dizziness, tremor, agitation, visual field defects, abnormal vision, diplopia Non-Neurological: nausea, vomiting, diarrhea, weight gain, skin rash	Enzyme Substrate: None Enzyme inducer: None Enzyme Inhibitor: None	No
Zonisamide	Na <sup>+</sup> channel inhibition	Partial	Neurological: sedation, dizziness, confusion, headache, psychosis Non-Neurological: Anorexia, renal stones, hypohydrosis	Enzyme Substrate: CYP 2C19, 3A4 Enzyme Inducer: None Enzyme Inhibitor: None	Yes

Legend: Ca<sup>2+</sup> = calcium ion, CYP = cytochrome P enzyme, GABA = gamma amino butyric acid, Na<sup>+</sup> = sodium ion, NMDA = N-methyl D-aspartic acid.

\* denotes skin rash risk (Steven's Johnson syndrome and Toxic Epidermal Necrolysis) related to Human Leukocyte Antigen (HLA)-phenotype.

Over the last decade newer antiepileptic drugs that have been approved for use by the Food and Drug Administration (FDA) in the treatment of epilepsy. While most newer antiepileptic drugs are approved as second line agents for the treatment of refractory seizures, topiramate, oxcarbazepine and lamotrigine are also approved for monotherapy in certain situations.<sup>6</sup>

According to the Biopharmaceutics Classification System (BCS), drugs are divided into four classes; high solubility/high permeability (Class I, optimal class with lowest risk of absorption variability), low solubility/high permeability (Class II), high solubility/low permeability (Class III) and low solubility/low permeability (Class IV).<sup>10</sup> A drug is considered to have high solubility when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1 to 7.5 at 37°C.<sup>11,12</sup> A drug is considered to be highly permeable when the extent of absorption (bioavailability) is  $\geq 90$  percent.<sup>11,12</sup> In 2000, the FDA started using the BCS to grant a waiver of *in vivo* bioavailability and bioequivalence testing of immediate release solid



dosage forms for Class I drugs.<sup>13</sup> The BCS classification for older and newer epilepsy medications is given in Table 4.<sup>11,14-27</sup>

**Table 4. Biopharmaceutics Classification System of antiepileptic medications<sup>11,14-27</sup>**

Antiepileptic Drugs	Solubility	Permeability	BCS class
<b>Older Antiepileptic Medications</b>			
Carbamazepine	Low	High	II
Clonazepam	Low	High	II
Ethosuximide	High	High	I
Phenobarbital	High	High	I
Phenytoin	Low	High	II
Primidone	Low	High	II
Valproic Acid	High	High	I
<b>Newer Antiepileptic Medications</b>			
Felbamate	Low	High	II
Gabapentin	High	Low	III
Lamotrigine	High	High	I
Levetiracetam	High	High	I
Oxcarbazepine	Low	High	II
Pregabalin	High	High	I
Tiagabine	High	High	I
Topiramate	High	High	I
Zonisamide	High	High	I

The comparative benefits and harms of older versus newer antiepileptic drugs have been assessed in numerous randomized controlled trials (RCT) with varying results. In the Standard And New Antiepileptic Drugs (SANAD) study, there were two treatment arms. In ‘Arm A’ carbamazepine was compared with other newer antiepileptic treatments (i.e. gabapentin, lamotrigine, topiramate, oxcarbazepine) while in ‘Arm B’ valproate was compared with newer antiepileptic agents (i.e. lamotrigine and topiramate). The efficacy, tolerability and safety of newer antiepileptic agents were compared with their older counterparts. In this RCT, lamotrigine significantly extended the time to treatment failure versus carbamazepine in patients with partial seizures but the time to treatment failure was similar between lamotrigine and valproate in patients with generalized seizures. However, other newer antiepileptic agents demonstrated similar or inferior 12-month remission rates as compared to older antiepileptics.<sup>28,29</sup>

Another important issue in the management of epilepsy surrounds generic substitution of innovator antiepileptic medications. The American Academy of Neurology has issued two position papers stating that there is concern with generic antiepileptic medication substitution and that physicians should specifically approve all generic substitutions.<sup>30,31</sup> The Italian League Against Epilepsy established a working group on generic products in epilepsy treatment. They concluded that generic medications offer a valuable and cost effective choice in the management of epilepsy but that generic substitution is not recommended in patients who achieve seizure remission on an innovator product.<sup>32</sup> The FDA and the American Society of Health-System Pharmacists do not share the view that antiepileptic medications, or other narrow therapeutic index medications (medications where the difference between the minimum effective and minimum toxic concentrations are close together), should be treated differently with regard to generic substitution.<sup>33-36</sup> However, their responses have been related to the process of



determining bioequivalence and therapeutic equivalence rather than specifically providing an evaluation of comparative effectiveness. As such, several states including Hawaii, Illinois, Tennessee, and Utah prevent automatic generic substitution for innovator antiepileptic medications and another 24 State legislatures (including California and New York) have discussed or are considering legislation preventing generic substitution.<sup>33,37-40</sup> A common example of legislation includes: “Would prohibit a pharmacist from substituting or interchanging any antiepileptic drug, brand or generic, without notification to both the prescribing physician and the patient or the patient’s representative.”<sup>40</sup> Variations include written consent from the prescriber and/or patient before substitution can occur.

Opponents of generic substitution of antiepileptic medications oppose it on one or more of the following reasons: bioequivalence studies mandated by FDA are in normal volunteers and not in patients with epilepsy, bioequivalence may occur in the fasting but not the fed state (unless food is known to affect absorption when both are required), the acceptable limit for variance (90 percent confidence interval for the maximum plasma concentration and area under the curve for the generic falls within 0.80 and 1.25 (i.e. 20 percent over or under) of the innovator medication) is not narrow enough, generics may be close enough to the innovator to be bioequivalent but not to another generic medication (if one generic consistently but predictably achieves higher concentrations than the innovator and another consistently but predictably achieves lower concentrations then the two generic medications may not be bioequivalent), and bioequivalence may be seen for a generic and innovator medication within a group of patients but not necessarily within each individual patient with epilepsy.<sup>33,41</sup>

Due to the inconclusive results of the SANAD study and other currently available studies, a comparative effectiveness review of the efficacy, tolerability and safety of older versus newer antiepileptic treatments are needed. Similarly, given the controversy surrounding generic substitution of antiepileptic medications, a comparative effectiveness review of the efficacy, tolerability and safety is needed.

## Objective

To perform a comparative effectiveness review of the efficacy, safety and tolerability of antiepileptic medications and to address the issue of generic substitution by qualitatively and/or quantitatively comparing older versus newer antiepileptic medications and comparing innovator antiepileptic medications to their generic counterparts.

## II. The Key Questions

**Question 1:** In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on health outcomes: mortality, hospitalizations, office/emergency department visits, composite endpoint (ambulance services, hospitalizations, or emergency department visits for epilepsy), health-related quality of life, seizures (time to first seizure, time to exit for trial due to lack of efficacy, proportion of seizure free patients, proportion of patients with seizure remission, breakthrough seizures, frequency of seizures), secondary seizure injury (fracture, laceration, head trauma, aspiration pneumonia), status epilepticus, loss of drivers license, and loss of employment?

**Question 2:** In patients with epilepsy, what is the comparative effectiveness/efficacy of antiepileptic medications on intermediate outcomes: pharmacokinetics, the comparative dose of medication needed to control seizures, and switchback rates?

**Question 3:** In patients with epilepsy, what is the comparative impact of antiepileptic medications on serious adverse events such as neurological adverse effects, hypotension, rash, suicidal ideation, mood and cognition, bone density, and cosmetic adverse effects?

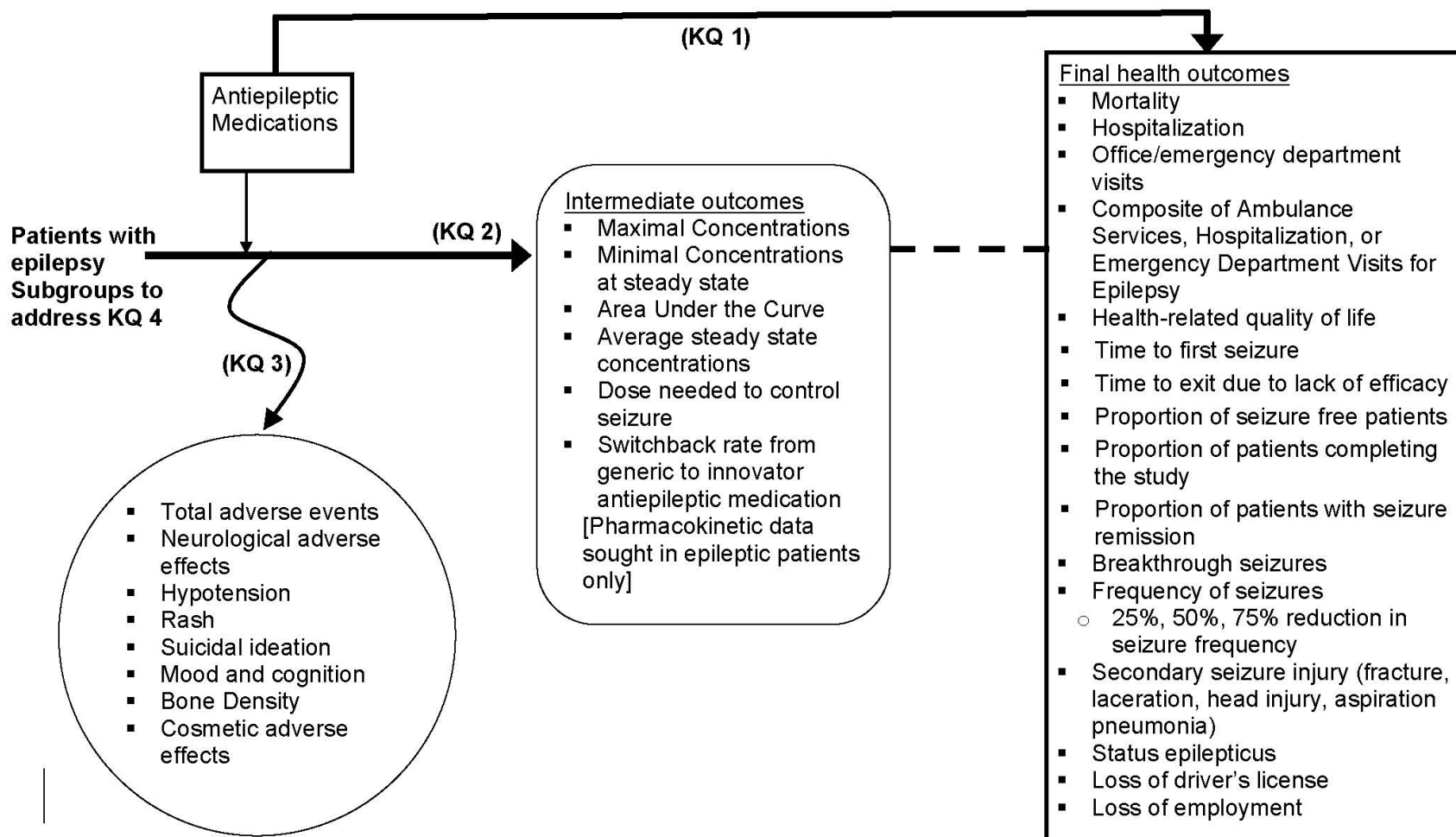
**Question 4:** In patients with epilepsy, what are the comparative benefits or harms for antiepileptic medications in subgroups of patients differentiated by seizure etiology (partial, generalized, specific epilepsy syndrome), seizure type (new onset disease, chronic disease), gender, ethnicity, patient age, and patient pharmacogenetic profile; and by types of antiepileptic medication (medication classes, individual medications and medications meeting the definition of having a narrow therapeutic index (BCS class II - IV)).

## Public Comment

The Draft Key Questions were posted for public comment. Based on the comments received and input from the Technical Expert Panel, the adverse events listed under KQ 3 was expanded to include bone mineral density and mood and cognition. We also clarified that we would look at frequency of seizures as a continuous variable but also as a categorical variable with 25 percent, 50 percent and 75 percent reductions in seizure frequency if such data are available.

### III. Analytic Framework

Proposed Analytic Framework for the Evaluation of Effect and Safety of Antiepileptic Medication in Patients with Epilepsy:



## IV. Methods

### Literature Search Strategy

Two independent investigators will conduct systematic literature searches of MEDLINE (from 1950 to the present) and the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews from the earliest possible date through the present. Each evaluation will have its own search strategy employed. The search for the older versus newer evaluation will utilize Cochrane's Highly Sensitive Search Strategy (Sensitivity Maximizing Version 2008) to limit to randomized controlled trials and the Scottish Intercollegiate Guidelines Network Observational Study Search Filter to limit to observational studies. The search for the innovator versus generic evaluation will contain no search filters. No language restrictions will be imposed in either search. A manual search of references from reports of clinical trials or review articles will be conducted. A search for ongoing studies will be conducted using the clinical trial registry at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Additionally, meeting abstracts will be screened from the following journals, *Epilepsia*, *European Journal of Neurology*, *Neurology*, *Annals of Neurology* and *Journal of Neurology*.

Detailed search strategies are provided in Appendix A.

### Study Selection

Studies will be included in the evaluation of key questions if they: (1) compare older antiepileptic medications to newer antiepileptic medications, compare innovator antiepileptic medications to generic antiepileptic medications, or compare an "A" rated generic medication to another "A" rated generic medication of the same type and dosage form; (2) are conducted in patients with epilepsy; and (3) report data on prespecified clinical or humanistic outcomes.

### Validity Assessment

Validity assessment will be performed using the recommendations in the [Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews](#). Each study will be assessed for the following individual criteria: comparable study groups at baseline, detailed description of study outcomes, blinding of subjects, blinding of outcome assessors, intent-to-treat analysis, description of participant withdrawals, and potential conflict of interest. Additionally, RCTs will be assessed for randomization technique and allocation concealment. Observational studies will be assessed for sample size, participant selection method, exposure measurement method, potential design biases, and appropriate analyses to control for confounding. Studies will then be given an overall score of good, fair, or poor. (Table 5) The rating system does not attempt to assess the comparative validity across different types of study design. For example, a "fair" RCT is not judged to have the same methodological criteria as a "fair" observational study. Both study design and quality rating should be considered when interpreting the methodological quality of a study.

**Table 5. Summary ratings of quality of individual studies**

Quality Rating	Definition
Good (low risk of bias)	Good studies have the least bias and results are considered valid. A study that adheres mostly to the commonly held concepts of high quality include the following: a formal randomized, controlled study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; and clear reporting of dropouts.
Fair	Fair studies are susceptible to some bias, but it is not sufficient to invalidate results. Fair studies do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	Poor studies have significant flaws of various types that may invalidate the results. Poor studies have serious errors in design, analysis, or reporting; large amounts of missing information, or discrepancies in reporting.

## Data Abstraction

Through the use of a standardized data abstraction tool, two reviewers will independently collect data, with disagreement resolved through discussion. The following information will be obtained from each trial, if applicable: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria, study population (including study inclusion and exclusion criteria, geographic setting, run-in period, study withdrawals, antiepileptic medication utilized, length of study, and duration of patient followup), patient baseline characteristics (gender, age, ethnicity), patient pharmacogenetic profile, seizure etiology (partial, generalized, specific epilepsy syndrome), seizure type (new onset, chronic disease), severity or stage of illness, types of antiepileptic medication (individual drug names, medication formulation, dose, schedule, bioequivalence status (if applicable), drug class, BCS class), comorbidities, and use of concurrent standard medical therapies. Intermediate, final health and adverse events (along with their definitions) will be collected if applicable including the event rate. Authors will be contacted for clarification or to provide additional data, if applicable.

Since there are two main topics being evaluated, we will differentiate the outcomes based on the following scheme:

- Outcome for older and newer antiepileptic evaluation
- Outcome for innovator and generic antiepileptic (or “A” rated generic versus another “A” rated generic antiepileptic) evaluation
- Common outcome for both older/newer and innovator/generic antiepileptic (or “A” rated generic versus another “A” rated generic antiepileptic) evaluations

The outcomes for the CER are as follows:

Comparative pharmacokinetics in those receiving therapy for epilepsy:

- Maximum concentration
- Minimum concentration at steady state

- Area under the curve
- Average steady state concentration

#### Comparative Efficacy:

- Time to first seizure
- Time to study exit due to lack of efficacy
- Proportion of seizure free patients
- Proportion of patients completing the study
- Proportion of patients achieving seizure remission
- Seizure frequency
- Incidence of breakthrough seizure
- Incidence of status epilepticus
- Dose needed to control seizures after switching from an innovator antiepileptic to its generic counterpart
- Secondary seizure injury (fracture, laceration, head trauma, aspiration pneumonia)

#### General Measures of Comparative Tolerance and Harms:

- Proportion of patients withdrawn due to adverse effects
- Cosmetic adverse events
- Incidence of adverse events
- Incidence of individual adverse events
- Incidence of adverse events resulting in therapy withdrawal
- Incidence of adverse events not resulting in therapy withdrawal
- Skin rash
- Neurological adverse events
- Suicidal ideation
- Health-related quality-of-life
- Mortality
- Medical service utilization
  - Office/emergency department visits
  - Hospitalizations
- Hypotension
- Harms specific to that particular antiepileptic medication
- Hospital stay duration
- Loss of drivers license
- Loss of employment
- Rates of switching from generic back to innovator medication for any reason

## Literature Synthesis

In the evaluation of older versus newer antiepileptic medications, each newer antiepileptic medication will be compared with an individual older epileptic medication. In the evaluation of



innovator and generic medications, each innovator antiepileptic drug will be compared to its corresponding generic medication separately. In the “A” rated generic medication versus another “A” rated generic medication evaluation, only “A” rated generics of the same drug and dosage form will be compared.

Upon review of available data for each outcome, those endpoints amenable for meta-analysis will be quantitatively synthesized and the rest will be qualitatively described in text and evidence tables. Single-arm observational studies, case series, or case reports will only be described qualitatively while randomized controlled trials and observational trials with a control group can be quantitatively synthesized or qualitatively described in text and evidence tables.

## Quantitative Analysis

Randomized controlled trials (RCTs) will be pooled separately from observational studies with a control group.

When pooling continuous endpoints, a weighted mean difference will be calculated using a DerSimonian and Laird random effects model.<sup>42</sup> In cases where mean change scores from baseline for each group are not reported, we will calculate the difference between the mean baseline and mean followup scores for each group. Standard deviations of the change scores will be calculated using the method proposed by Follman and colleagues.<sup>43</sup>

For dichotomous endpoints, weighted averages will be reported as relative risks with associated 95 percent confidence intervals. As heterogeneity between included studies is expected, a DerSimonian and Laird random-effects model will be used when pooling data and calculating relative risks and 95 percent confidence intervals.

Statistical heterogeneity will be addressed using the  $I^2$  statistic to assess the degree of inconsistency not due to chance across studies and ranges from 0 -100 percent with values of 25 percent, 50 percent and 75 percent representing low, medium and high statistical heterogeneity, respectively. Visual inspection of funnel plots and Egger’s weighted regression statistics will be used to assess the presence of publication bias.

Statistics will be performed using StatsDirect statistical software, version 2.4.6 (StatsDirect Ltd, Cheshire, England). A p-value of <0.05 will be considered statistically significant for all analyses.

In the event that there is more than one newer antiepileptic drug being compared with an older antiepileptic drug, each newer antiepileptic drug will be compared individually against the older antiepileptic drug (as a separate trial) by dividing the older antiepileptic drug group equally between the comparisons.<sup>44</sup> In the event that there is more than one generic antiepileptic drug group being compared with an innovator antiepileptic drug group, each generic antiepileptic drug will be compared individually against the innovator antiepileptic drug (as a separate trial) by dividing the innovator antiepileptic drug group equally between the comparisons.<sup>44</sup>

## Subgroup and Sensitivity Analyses

We will conduct subgroup and sensitivity analysis to assess the heterogeneity of our meta-analyses’ conclusions.

In subgroup analyses for the older versus newer evaluation, we will evaluate the results in those with new onset versus chronic (refractory) disease. We will also evaluate results separately based on the seizure type: partial, generalized, and specific epilepsy syndrome. If possible, trials and studies in absence seizures will also be separated from other generalized seizure types.

In subgroup analyses for the innovator versus generic evaluation, innovator medications will be specifically studied against known “A” rated generics, and innovator medications within a BCS class (I, II, or III) will be compared to their corresponding generic medications within that same class.

In both the older versus newer and innovator versus generic evaluations, we will perform subgroup analyses based on gender, ethnicity, patient age, and patient pharmacogenetic profile.

## Grading the Strength of Evidence

We will use EPC methodology based on the criteria and methods of GRADE (Grading of Recommendations Assessment, Development and Evaluation) to assess the strength of evidence. The GRADE system uses four required domains – risk of bias, consistency, directness, and precision.<sup>45</sup> Additional domains will not be utilized because they are deemed not relevant to this review. All assessments will be made by two investigators (with disagreements resolved through discussion). The evidence pertaining to each key question will be classified into five broad categories: (1) “high”, (2) “moderate”, (3) “low”, (4) “very low” grade, or (5) “insufficient”. (Table 6) Below we describe in more detail the features that determine the strength of evidence for the different outcomes evaluated in this report.

**Table 6. Definitions for grading the strength of evidence**

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Very low confidence that the evidence reflects the true effect. Any estimate of effect is very uncertain.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect

## Risk of Bias

Risk of bias is the degree to which the included studies for any given outcome or comparison has a high likelihood of adequate protection against bias. The risk of bias will be assessed through the evaluation of both design and study limitations. To assess study design, we will record if the study was a randomized controlled trial or an observational study. To assess study design, we will rank studies as having no limitations, serious limitations, or very serious limitations.

## Consistency

Consistency is the degree of similarity in the direction of the effect sizes from studies included in an evidence base. Consistency will be assessed in two main ways, first the effect

sizes with the same sign will be on the same side of unity and second the range of effect sizes will be narrow. The domain of consistency will be used to rank studies as having no inconsistency, serious inconsistency, and very serious inconsistency. For outcomes whereby only a single study was included, consistency will not be judged. We will also consider measures of heterogeneity from our meta-analyses in evaluating consistency.

### **Directness**

Directness refers to whether the evidence links the compared interventions directly with health outcomes, and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We will rank the directness domain as follows: no indirectness, serious indirectness, and very serious indirectness.

### **Precision**

Precision refers to the degree of certainty surrounding an effect estimate with respect to a given outcome. For example, when a meta-analysis is performed, we will evaluate the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one with a confidence interval wide enough to include clinically distinct conclusions (e.g. both clinically important superiority and inferiority), a circumstance that will preclude a conclusion.

### **Rating Applicability**

Effectiveness studies will meet five of the following seven criteria: primary care population, less stringent eligibility criteria, assessed final health outcomes, adequate study duration with clinically relevant treatment modalities, assessed adverse events, had an adequate sample size, and used intention to treat analysis.<sup>46</sup> Studies meeting less than 5 criteria would be classified as efficacy trials and be deemed to have less applicability. In addition, factors identified in Table 7 are important when determining applicability and will be extracted into evidence tables for every study. Given these inputs, the applicability of each study will be determined. Using all of the studies to answer a key question, the applicability of the body of evidence will be determined and reported qualitatively.



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**Table 7. Applicability PICOTS and data to extract**

<b>Feature</b>	<b>Condition that limits applicability</b>	<b>Features to be extracted into evidence table</b>
Population	Differences between patients in study and the community	Eligibility criteria, demographics (age, gender, race, ethnicity, types of seizure disorders)
Population	Narrow or unrepresentative severity or stage of illness	Severity or stage of illness (referral or primary care population)
Population	Events rates markedly different than in community	Event rates in treatment and control groups
Intervention	Regimen not reflective of current practice	Medication formulation (immediate versus sustained release), dose, schedule, duration
Comparator	Use of substandard alternative therapy	Medication formulation, dose, schedule, duration, bioequivalence (if applicable)
Outcomes	Surrogate endpoints, brief followup periods, improper definitions for outcomes, composite endpoints	Outcomes (benefits and harms) and how they were defined
Settings	Settings where standards of care differ markedly from setting of interest	Geographic setting

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## VI. Abbreviations

Abbreviation	Definition
“A” Rated generic	Generic drug that is equivalent to the brand name product in safety and effectiveness as determined by FDA
BCS	Biopharmaceutics Classification System
Ca <sup>2+</sup>	Calcium ion
CYP	Cytochrome P enzyme
FDA	Food and Drug Administration
GABA	Gamma Amino Butyric Acid
Na <sup>+</sup>	Sodium ion
NMDA	N-methyl D-aspartic acid
RCT	Randomized Controlled Trial
SANAD	Standard And New Antiepileptic Drugs

## VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

**NOTE: The following protocol elements are standard procedures for all protocols.**

## VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

## IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

## X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.



## Appendix A: Search Strategies

/ after an index term indicates that all subheadings were selected.  
\* before an index term indicates that that term was focused (i.e. limited to records where major MeSH/Emtree term)  
"exp" before an index term indicates that the term was exploded.  
.tw. indicates a search for a term in title/abstract.  
.mp. indicates a free text search for a term.  
.pt. indicates a search for a publication type.  
\$ at the end of a term indicates that this term has been truncated.  
? in the middle of a term indicates the use of a wildcard.  
adj indicates a search for two terms where they appear adjacent to one another.  
sh indicates a search term for subheading.

### Search 1: Older versus Newer

#### MEDLINE (OVID)

1. Epidemiologic studies/
2. Exp case control studies/
3. Exp Cohort Studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. cohort analy\$.tw.
7. (follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. longitudinal.tw.
10. retrospective.tw.
11. cross sectional.tw.
12. Cross-Sectional Studies/
13. Or/1-12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. Or/14-21
23. animals.sh not (humans.sh. and animals.sh.)
24. 22 not 23
25. 13 or 24
26. felbamate.mp.

27. gabapentin.mp.
28. lacosamide.mp.
29. lamotrigine.mp.
30. levetiracetam.mp.
31. oxcarbazepine.mp.
32. pregabalin.mp.
33. rufinamide.mp.
34. tiagabine.mp.
35. topiramate.mp.
36. vigabatrin.mp.
37. zonisamide.mp.
38. Or/26-37
39. Epilepsy/ or epilepsy.mp.
40. epilep\$.mp.
41. seiz\$.mp
42. convuls\$.mp.
43. Or/39-42.mp.
- 44. 25 and 38 and 43**

#### **CENTRAL (OVID)**

1. felbamate.mp.
2. gabapentin.mp.
3. lacosamide.mp.
4. lamotrigine.mp.
5. levetiracetam.mp.
6. oxcarbazepine.mp.
7. pregabalin.mp.
8. rufinamide.mp.
9. tiagabine.mp.
10. topiramate.mp.
11. vigabatrin.mp.
12. zonisamide.mp.
13. Or/1-12
14. Epilepsy/ or epilepsy.mp.
15. epilep\$.mp.
16. seiz\$.mp
17. convuls\$.mp.
18. Or/14-17.mp.
- 19. 13 and 18**

## Search 2: Innovator versus Generic

### MEDLINE (OVID)

1. generic.mp.
2. innovator.mp.
3. nonproprietary.mp.
4. drugs, generic/
5. therapeutic equivalency/
6. (brand adj name).mp.
7. Or/1-6
8. Epilepsy/ or epilepsy.mp.
9. epilep\$.mp.
10. seiz\$.mp.
11. convuls\$.mp.
12. Or/8-11
13. **7 and 12**

### CENTRAL (OVID)

1. generic.mp.
2. innovator.mp.
3. nonproprietary.mp.
4. drugs, generic/
5. therapeutic equivalency/
6. (brand adj name).mp.
7. Or/1-6
8. Epilepsy/ or epilepsy.mp.
9. epilep\$.mp.
10. seiz\$.mp.
11. convuls\$.mp.
12. Or/8-11
13. **7 and 12**