Evidence-based Practice Center Systematic Review Protocol

Project Title: *Management of Infantile Epilepsy*

Initial Publication Date: February 3, 2021
Amendment Dates: February 17, 2021, March 7, 2021
(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

The Patient-Centered Outcome Research Institute (PCORI) is collaborating with the Agency for Healthcare Research and Quality (AHRQ) to conduct a systematic evidence review on interventions for infantile epilepsy. This review will enable the American Epilepsy Society (AES) to disseminate the most current evidence to stakeholders engaged in research and clinical care of infants and children from birth to under three years of age and will inform AES considerations of appropriate clinical guidance on this important topic.

Seizures are episodes of abnormal electrical activity in the brain, which can manifest clinically in various forms. The incidence of infantile epilepsy is approximately 70-100/100,000 during the first year of life and around 65/100,000 per year between age one and four.[1] Current data in resource-rich countries suggests epilepsy disproportionately affects children under three years of age compared to any other age groups.[1,2] In this age group, epilepsy differs greatly from epilepsy in older children or adults, specifically regarding etiology, clinical presentation, electroencephalogram patterns, and medical management.[2] Uncontrolled seizures in children 0 to 3 years old may lead to significant developmental, behavioral and psychological impairments. However, treating seizures may cause adverse effects and harms that may also contribute to delayed development or reduced cognitive function. Thus, providers and caregivers must balance seizure control with the potential harms of epilepsy treatment.[3]

Despite the importance of managing seizures in this young population, key evidence gaps remain regarding optimal treatment. In 2015, the International League Against Epilepsy (ILAE) Commission of Pediatrics released a consensus document of recommendations for the management of infantile seizures.[1] The report concluded that none of the contemporary antiseizure medications (ASMs) used to treat infant epilepsy are supported by high-quality evidence.[1] Other systematic reviews on epilepsy, including a 2020 update by the National Institute for Health Care Excellence (NICE), have focused on the broader population of children, adolescents, and adults, without focusing on patients less than three years of age.[3] To address these important evidence gaps, this systematic review will focus on treatment of epilepsy in children age 1 month to <3 years. Specifically, we will address the comparative effectiveness of pharmacologic interventions, dietary interventions, surgical interventions, neurostimulation, and gene therapy for selected conditions.

Purpose of the Systematic Review

This systematic review aims to identify studies addressing management of epilepsy for children 1 month to <3 years of age (36 months old or less). We will assess the effectiveness, comparative effectiveness, and harms for each intervention to support potential development of a clinical practice guideline. In addition, given the young age of the patients, their caregivers play a key role in the management process. As such, we will identify literature reporting on caregiver issues such as anxiety. We will also investigate quality-of-life outcomes (including those of caregivers) to inform the tradeoffs among different interventions.

II. The Key Questions

The following key questions specify the scope of this small systematic review.

Key Question 1. What is the effectiveness and comparative effectiveness of pharmacologic treatments for infantile epilepsy (infants age 1 month to <3 years)?

Key Question 2. What is the effectiveness and comparative effectiveness of non-pharmacologic treatments for infantile epilepsy (e.g., dietary therapies, surgery, and brain stimulation therapies), including comparisons to other non-pharmacologic and/or pharmacologic therapies?

Key Question 3. What are the harms or comparative harms of treatments for infantile epilepsy?

Table 1: PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting)

	Inclusion	Exclusion
Population	• Infants (1 month to <3 years) diagnosed with epilepsy • Subpopulations based on baseline seizure severity/frequency, history of previous treatment, length of gestation	• West syndrome/infantile spasms • Non-epileptic seizures • Provoked seizures, including febrile seizures • Metabolic epilepsies • Status epilepticus • Acute symptomatic seizures
Intervention	• KQ 1, 3: Pharmacologic interventions • KQ 2, 3: Non-pharmacologic intervention: dietary therapies, surgery, brain stimulation, and gene therapy	• Diagnostic research • Provider/organization level interventions such as awareness campaigns • Metabolic therapies • Vitamin therapies • Social and community services
Comparator	• KQ1: Other pharmacologic interventions or usual care • KQ2: Other pharmacologic or non-pharmacologic interventions or usual care • KQ3: Inclusive of comparators for KQ1&2	
Outcomes	• All-cause mortality • SUDEP • Hospitalization	

	Inclusion	Exclusion
	• Seizure freedom • Seizure frequency • Seizure severity (including seizure duration, seizure burden, and status epilepticus) • Engel classification • Progression to other seizure types or syndromes (e.g., infantile spasms, Lennox-Gastaut Syndrome) • Time to seizure remission • Neurodevelopment • Quality of life (including eating) • Sleep outcomes (e.g., total time spent asleep at night) • Behavioral function • Cognitive function • Functional performance (including school) • Social function • Caregiver anxiety • Caregiver quality of life • General health status • Cost of treatment • Adverse events (infection, new neurological deficits, surgical complications, irritability, somnolence, dizziness, drug toxicity, etc.)	
Timing	Effectiveness: 12 week minimum follow-up Harms: No minimum follow-up	
Setting	Setting not limited	

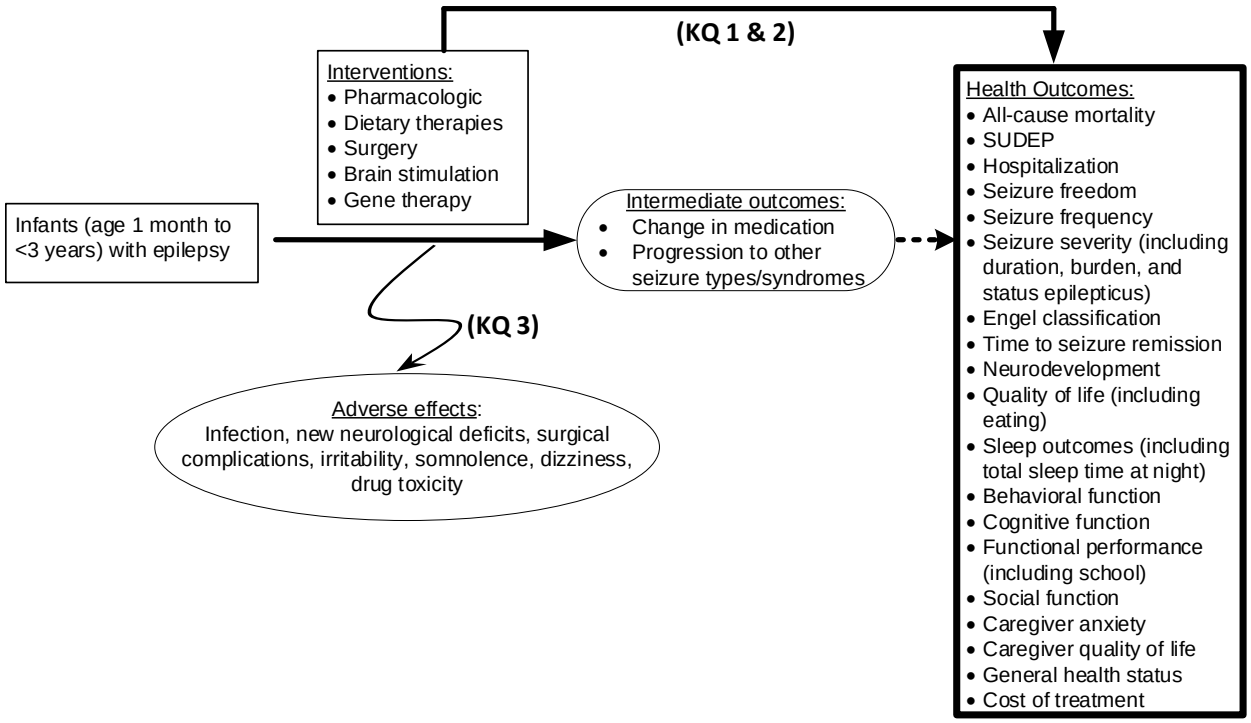
In addition to the Key Questions listed above, this review will also address two Contextual Questions:

CQ1. What are the parental preferences for treatment options for infantile epilepsy?
CQ2. What are the harms or comparative harms of not treating infantile epilepsy?

We plan to address these questions in the review's Discussion section, referring to evidence discovered during the review process.

III. Analytic Framework

Figure 1. Analytic Framework for Management of Infantile Epilepsy



IV. Methods

Criteria for Study Inclusion and Exclusion

As suggested in the Agency for Healthcare Research and Quality (AHRQ) EPC Methods Guide for Comparative Effectiveness Reviews, we list the inclusion criteria separately for several categories: publication type, study design, patient characteristics, intervention characteristics, setting, and outcome data.[4]

Publication Criteria

1. **Full-length articles.** The article must be published as a full-length, peer-reviewed study. We will not include abstracts or meeting presentations because they do not include sufficient details about experimental methods to permit an evaluation of study design and conduct; they may also contain only a subset of measured outcomes.[5,6] Additionally, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies when compared with the final study publication or to describe studies that are never published as full articles.[7-10]
2. **Publication date.** We will include studies published from 1999 to present. Earlier articles are unlikely to reflect current practice.

3. **Redundancy.** To avoid double-counting patients, when several reports of overlapping patients are available, we will only include outcome data from the report with the largest number of patients. We will include data from a smaller publication when it reports data on an included outcome that was not provided by the largest report or reports longer follow-up data for an outcome.
4. **English language.** The compressed timeframe for this review does not permit translation of non-English language articles.

Study Design Criteria

1. We will only include empirical studies; thus, we will exclude reviews, letters, guidelines, position statements, and commentaries. We will only use systematic reviews to identify empirical studies, as a supplement to the full literature search described in the section below entitled Literature Search Strategy.
2. We will exclude studies of diagnosis as well as studies of provider/organization interventions such as awareness campaigns.
3. For single-treatment effectiveness in Key Questions 1 and 2, we will employ a staged approach. Specifically, we will first require that studies must have two or more separate groups of patients, one of which received inactive treatment such as placebo or sham (in order to measure effectiveness). We will not require that patients be randomized to groups, nor will we require that studies plan their comparison(s) prospectively. If, for a given treatment, there are no such studies, we will then examine pre-post studies of that treatment. For pre-post studies, we will require that authors report baseline seizure frequency as well as follow-up seizure frequency.
4. For comparative effectiveness in Key Questions 1 and 2, we will require that studies directly compare two or more management strategies.
5. For Key Question 3 (harms), we will include single-arm studies as well as controlled studies.
6. To be included for any Key Question, the study must report outcome data on at least 30 patients in each group. We made an exception for studies of surgical interventions, for which we only required at least 10 patients per surgical procedure.

Patient Criteria

1. At enrollment, infants (age 1 month to <3 years) must have a diagnosis of epilepsy. We will not require EEG confirmation of seizures for inclusion.
2. At enrollment, patients must not have had febrile seizures or infantile spasms or West Syndrome as their primary diagnosis. We will exclude patients being treated primarily for the following conditions at enrollment: non-epileptic seizures, metabolic seizures, or other seizures not due to epilepsy. In addition, as this review is intended to focus primarily on non-acute management of epilepsy, we will exclude patients treated for status epilepticus. At least 80% of patients must have been experiencing seizure types of interest (e.g., partial seizures) at the time of treatment.

3. For the age of enrolled patients, we require either that 1) studies enroll a population for which at least 80% were age 1 month to <3 years), or 2) that studies report data specifically for this age group.

Intervention Criteria

1. Active interventions must have been one of specific treatments listed in Table 2 below. We will exclude studies that only reported outcome data for a heterogeneous set of treatments (e.g., different infants receiving different pharmacologic agents, or infants undergoing different surgical procedures).
2. For dietary interventions (e.g., ketogenic diet), we will require studies to report either confirmation of dietary components by the study administrator, or that parents were educated in advance about what the diet involves. Thus, we will exclude studies of dietary interventions if the usage of the diet was based solely on parent report.
3. For gene therapy, we will only include treatment for the following conditions: Dravet Syndrome, Angelman syndrome, and Rett syndrome.

Setting Criteria

1. Any setting.

Data Criteria

1. The study must report data pertaining to one of the outcomes of interest (see outcome list in Table 1). The review team consulted the Core Outcomes Set for epilepsy when revising this outcome list.[11]
2. For seizure frequency, the data must have been collected prospectively (e.g., a prospective study itself, or a retrospective study in which parents completed a diary prospectively).
3. For effectiveness/comparative effectiveness, we will only include studies with follow-up duration of 12 or more weeks. However, for harms data, we will extract data from all reported time points.

Table 2: Included Interventions

Category	Interventions	Interventions	Interventions
Pharmacological	Brivaracetam	Felbamate	Pregabalin
	Cannabidiol	Fenfluramine	Primidone
	Carbamazepine	Gabapentin	Rufinamide
	Clobazam	Lacosamide	Stiripentol
	Clonazepam	Lamotrigine	Tiagabine
	Diazepam	Levetiracetam	Topiramate
	Divalproex	Oxcarbazepine	Valproate
	Eslicarbazepine	Perampanel	Vigabatrin
	Ethosuximide	Phenobarbital	Zonisamide
	Everolimus	Phenytoin	

Category	Interventions	Interventions	Interventions
Dietary therapy	Ketogenic diet	Low glycemic index	Medium-chain triglyceride diet
	Modified Atkins	Modified ketogenic diet	
Surgery	Corpus callosotomy	Hemispherectomy/ Hemispherotomy	Resective surgery
	Laser ablation	Multiple subpial transections	
Brain stimulation	Vagus nerve stimulation		
Gene therapy	Gene therapy only for Dravet syndrome, Angelman syndrome, or Rett syndrome		

Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Literature searches will be performed by Medical Librarians at the Evidence-based Practice Center (EPC) Information Center, and will follow established systematic review protocols. We will search the following databases using controlled vocabulary and text words: EMBASE, MEDLINE, PubMed, and The Cochrane Library. The search strategy appears in Appendix A, and will not be peer reviewed. We will update the search during peer review.

The following gray literature sources will be searched using text words: ClinicalTrials.gov, Centers for Disease Control and Prevention (CDC), Medscape, National Academy of Medicine, the United States Food and Drug Administration (FDA), and the Web sites of relevant organizations (e.g., Agency for Healthcare Research and Quality [AHRQ], American Society for Parenteral and Enteral Nutrition (ASPEN), and Academy of Nutrition and Dietetics (AND). Hand searches of published systematic reviews will be used to identify any studies missed by searches. We will not contact study authors for additional data not provided in their publications, as in our experience, such efforts typically yield little. We will also search gray literature, and will set up a Supplemental Evidence And Data for Systematic review (SEADS) portal so that interested parties can submit additional data that might meet our inclusion criteria.

Literature screening will be performed in duplicate using the database Distiller SR (Evidence Partners, Ottawa, Ontario, Canada). Literature search results will initially be screened for relevance. Relevant abstracts will be screened against the inclusion and exclusion criteria in duplicate. Studies that appear to meet the inclusion criteria will be retrieved in full and screened again in duplicate against the inclusion and exclusion criteria. All disagreements will be resolved by consensus discussion between the two original screeners. The literature searches will be updated during the Peer Review process, before finalization of the review.

Data Abstraction and Data Management

Data will be abstracted using Microsoft Word and Excel. Elements to be abstracted include: general study characteristics (e.g., study design, country, setting, enrolled number of patients,

length of follow-up); patient characteristics (e.g., age, age dispersion, sex, specific diagnoses, concomitant treatments); intervention details (doses of medications, dietary regimens, surgical procedures, brain stimulation parameters); outcome data; and risk of bias items.

Assessment of Methodological Risk of Bias of Individual Studies

We define risk of bias as the risk that a study's point estimate of the effect size is inaccurate. For any outcomes that will receive strength-of-evidence (SOE) grades (see pertinent section below), we will assess the risk of bias (which is one of several inputs to the SOE). We will assess randomized trials for Key Question 1 and 2 using the Cochrane Risk of Bias 2 (ROB2) tool.{1131669} The domains of ROB2 are:

- Randomization process
- Deviations from intended interventions
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

For nonrandomized studies for Key Question 1 and 2, we will use the Risk of Bias in Non-randomized Studies (ROBINS-I) tool.{1061678} The domains of ROBINS-I are:

- Confounding
- Selection of participants into the study
- Classification of interventions
- Deviations from intended interventions
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

We will use the items to categorize each outcome of each study as either Low, Moderate, or High risk of bias. This categorization will not be based on a numerical score, but rather will be a subjective judgment based on the items assessed. Due to the subjectivity, two raters will independently assess risk of bias of each study, with disagreements resolved by discussion.

Data Synthesis

For studies reporting on health outcomes, we plan to perform meta-analysis when appropriate and possible. Decisions about whether meta-analysis is appropriate will depend on the judged clinical homogeneity of the different study populations, research designs, and outcomes. However, we anticipate that meta-analysis is likely to be inappropriate given the heterogeneity of the literature base. Thus, we anticipate performing a narrative synthesis. This narrative synthesis will address study designs as well as risk of bias. We may employ additional categorizations of the evidence. For example, studies that compare two treatments directly will be discussed separately from studies that compare different timings of treatment initiation.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

For Key Questions 1 and 2 of this review, we consider the following eight outcomes "major" and therefore will rate their strength of evidence (SOE):

- All-cause mortality
- SUDEP
- Hospitalization
- Seizure freedom
- Seizure frequency
- Quality of life
- Caregiver quality of life
- Adverse effects

These outcomes were chosen by the review team after consultation with our subject matter experts and we also solicited input from the technical expert panel (TEP). We will grade the SOE based on the EPC Methods Guide recommendations.[4] The primary domains assessed include risk of bias, directness, consistency, precision, and reporting bias. Additional domains may be used when appropriate, including dose-response association, strength of association, and the possibility that controlling for plausible confounders would increase the effect size. For quality control, two reviewers will judge each domain independently, and they will meet to resolve discrepancies. The output of the domain ratings is a rating of the SOE: high, moderate, low, or insufficient. This rating is made separately for each outcome of each comparison of each KQ. To assist the domain judgments, where available, we will use the minimal important difference (MID) for each of the eight rated outcomes. To identify MIDs for major outcomes, we sought input from our SMEs and TEP.

We will assign an SOE rating of Insufficient when the evidence does not permit a conclusion for the outcome of interest for that KQ. If the evidence is sufficient to permit a conclusion, the rating is deemed high, moderate, or low. In such cases, if the difference is statistically significant, we will conclude that there is a difference, where as if the difference is not statistically significant, we will conclude that there is no important difference (only when the 95% confidence interval is narrow enough to rule out the minimal important difference for that outcome). The rating will be based on considering all of the domains listed below. Below, we discuss the primary domains and how we will assess them:

Risk of bias (see the above section entitled *Assessment of Methodological Risk of Bias of Individual Studies*). This concerns internal validity: the extent to which a difference in post-treatment outcomes can be attributed to the treatments themselves rather than other factors. If the evidence permits a conclusion, then, all else being equal, a set of studies at low risk of bias yields a higher SOE rating than a set of studies at moderate or high risk of bias.

Directness. Directness relates to (a) whether evidence links interventions directly to a health outcome of specific importance for the review, and (b) for comparative studies, whether the comparisons are based on head-to-head studies.

Consistency. Consistency is the degree to which included studies find either the same direction or similar magnitude of effect.

Precision. Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size, number of events, and width of confidence intervals relative to a clinically important effect estimate.

Reporting bias. Reporting bias will be addressed by examining the funding source of included studies, the direction and magnitude of effects identified in included studies, and noting the presence of abstracts or ClinicalTrials.gov entries describing studies that did not subsequently appear as full-length published articles.

Applicability

Several factors may limit the applicability of findings, including the extent to which the results from included studies may or may not apply to the full spectrum of patients, interventions, and comparators for this clinical area. Based on EPC guidance,[4] the SOE rating will be uninfluenced by these factors. Instead, we will discuss applicability in a separate section.

V. References

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VI. Definition of Terms

Term	Definition
ACTH	Adrenocorticotropic Hormone
AES	American Epilepsy Society
ASM	Antiseizure medications
ILAE	International League Against Epilepsy
NICE	National Institute for Health and Care Excellence
PCORI	Patient-Centered Outcomes Research Institute
SCN2A	One of the genes most commonly associated with early epilepsy
SUDEP	Sudden Unexpected Death in Epilepsy

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
2/17/21	Table 1, page 2, population row, inclusion criteria cell.	Subpopulations based on baseline seizure severity/frequency, history of previous treatment, length of gestation	Subpopulations based on baseline seizure severity/frequency, history of previous treatment, length of gestation and demographic characteristics such as race/ethnicity	Equity considerations are a priority for the Executive Branch and the Department of HHS. The change will allow the evidence review to study if racial/ethnic disparities exist in enrollment in infantile epilepsy effectiveness studies as well as in potential differences in the effectiveness of interventions included in the evidence review.
3/7/2021	Title and Key Questions and Contextual Questions	“epilepsy”	“epilepsies”	Edit to acknowledge explicitly that epilepsy is not a single disease (this was based on a comment received from the Pediatric Epilepsy Research Consortium)

Date	Section	Original Protocol	Revised Protocol	Rationale
3/7/2021	Criteria for Study Inclusion and Exclusion, Study Design Criterion #3	"For pre-post studies, we will require that authors report baseline seizure frequency as well as follow-up seizure frequency"	We removed this sentence	Some prepost studies report rates of seizure freedom, not prepost seizure frequencies, and we believe this is sufficiently relevant to include
3/7/2021	Criteria for Study Inclusion and Exclusion, Study Design Criterion #6	Allow outcome data on 10-29 patients only for surgery studies	Expand this criterion to RCTs	Some RCTs of diets enrolled 10-29 patients and we felt the evidence was important enough to include
3/7/2021	Criteria for Study Inclusion and Exclusion, Patient Criterion #1 and #3	Age 1 month to < 3 years	Changed to Age 1 month to <=36 months	This is for clarity, since some may interpret 3 years to include those aged 37-47 months.
3/7/2021	Criteria for Study Inclusion and Exclusion, Data Criteria	"For seizure frequency, the data must have been collected prospectively (e.g., a prospective study itself, or a retrospective study in which parents completed a diary prospectively)."	Criterion deleted	This criterion seemed too restrictive to us, particularly for the surgical literature which is almost exclusively retrospective

Date	Section	Original Protocol	Revised Protocol	Rationale
3/7/2021	Assessment of Methodological Risk of Bias of Individual Studies	One instrument for RCTs, and another instrument for all other designs	Two instruments for nonRCTs: one for studies with control groups, and one for studies without control groups	ROBINS-I was designed for studies with control groups, so we will only use it for non-randomized studies with control groups. For uncontrolled studies, we will use items from EPC guidance.
3/7/2021	End of the section on Assessment of Methodological Risk of Bias of Individual Studies	Risk of bias assessed for all outcomes	Clarify that risk of bias need only be assessed for outcomes receiving Strength of Evidence grades	Since less important outcomes will not receive Strength of Evidence grades, we believe it is not necessary to rate their risk of bias.

VIII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing of the public comments and seeking input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the Key Questions are specific and relevant. A summary of the four public comments appears next.

The American Association of Neurological Surgeon/Congress of Neurological Surgeons (AANS/CNS) Joint Guidelines Review Committee (JGRC) sent the protocol to its Pediatric Neurological Surgery section to review. On August 13th, 2020, they stated they found the protocol adequate to proceed.

Greenwich Research Ltd. submitted comments on August 13th, 2020. Primarily, while they support the effort of the systematic review to assess the effectiveness and risk of interventions

for infantile epilepsy, they requested a differentiation of seizure etiologies. They commented that this would allow a more targeted analysis of the various interventions and their effectiveness.

The National Association of Epilepsy Centers (NAEC) submitted their comment on August 13th, 2020. Similar to the comments submitted by Greenwich Research Ltd., they emphasized the importance of distinguishing different syndromes and etiologies, as they respond to various treatments differently. The NAEC also submitted additional comments specific to the key questions. On Key Question 1, they stated a need to separate neonates from infants, as well as a need to specify various etiologies. On Key Question 2, they noted the importance of including cost-effectiveness into the analysis. They also commented the importance to investigate inequality and disparities as it relate to the comparison described.

An anonymous commented submitted on July 30th, 2020 highlighted the need to include cost, relative cost, and cost savings of the interventions to address the rising healthcare cost and its impact.

IX. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XIII. Role of the Funder

This project was funded by the Patient Centered Outcomes Research Institute under Contract No. 75Q80120D00002 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services by the Patient- Centered Outcomes Research Institute (PCORI) through a memorandum of Agreement Amendment, number 20-603M-19. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Patient Centered Outcomes Research Institute or the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A: Search Strategy

Embase.com Strategy: (Combines Medline and EMBASE) 1/1/1999 - 11/20/2020

Set	Concept	Search statement
1	Childhood Epilepsy	'benign childhood epilepsy'/exp OR 'childhood absence epilepsy'/exp OR 'severe myoclonic epilepsy in infancy'/exp OR (dravet* NEXT/1 (disease OR syndrome))
2	Epilepsy/ 0-3 Age Group	[infant]/lim OR [newborn]/lim OR newborn/exp OR [preschool]/lim OR 'preschool child'/exp OR toddler/exp OR (babies OR baby OR child*:ti OR infan* OR neonat* OR newborn* OR nicu OR paediatric* OR pediatric* OR preschool* OR toddler* OR 'very young'):ab,ti,kw OR ('younger than' OR under OR below) NEAR/3 (3 OR three) OR (3 OR three) NEAR/3 ('or below' OR 'or under' OR 'or younger') AND ('epilepsy'/exp OR 'epileptic patient'/exp OR epilep*:ti)
3	Infantile Spasm	'infantile spasm'/exp OR ((infan* OR neonat* OR newborn*) NEAR/2 (convuls* OR seizure* OR spasm*)):ab,ti,kw
4	Neonatal Seizure	([infant]/lim OR [newborn]/lim OR newborn/exp OR (babies OR baby OR infan* OR neonat* OR newborn* OR nicu):ab,ti,kw) AND ('febrile convulsion'/exp OR seizure/exp OR (convuls* OR spasm* OR seizure*):ab,ti,kw)
5	Pharmacologic/ Vitamin Treatment	acetazolamide OR acth OR 'adrenocorticotropic hormone' OR benzodiazepine* OR brivaracetam OR bromide OR cannabidiol OR carbamazepine OR clobazam OR clonazepam OR clorazepate OR corticotropin OR divalproex OR eslicarbazepine OR ethosuximide OR everolimus OR felbamate OR fenfluramine OR folate OR 'folic acid' OR frisium OR gabapentin OR lacosamide OR lamotrigine OR levetiracetam OR liposteroid OR lorazepam OR mesuximide OR methsuximide OR onfi OR oxcarbazepine OR perampanel OR phenobarbital OR phenytoin OR prednisone OR pregabalin OR primidone OR pyridoxine OR 'pyridoxal 5 phosphate' OR rufinamide OR sabril OR stiripentol OR thiopental OR thiopentone OR tiagabine OR topiramate OR valproate OR 'valproate semisodium' OR 'valproic acid' OR vigabatrin OR zonisamide
6	Diet Therapy	'ketogenic diet'/de OR (keto* OR ketogenic OR 'low glycemic index' OR 'medium chain triglyceride' OR 'modified atkins' OR 'modified keto' OR 'modified ketogenic'):ab,ti,kw

7	Surgical Procedures	craniotomy/de OR hemispherectomy/de OR 'laser surgery'/de OR lobectomy/de OR 'corpus callosotomy' OR craniotom* OR (disconnect* NEAR/3 (hemispher* OR surg* OR procedure*)) OR hemispherecotom* OR hemispherotom* OR lesionectom* OR lobectom* OR (laser* NEAR/3 (ablat* OR operat* OR procedure* OR surg*)) OR (multilobar NEAR/3 disconnect*) OR (palliat* NEAR/3 operat* OR procedure* OR surg*) OR resect* OR resection OR transect* OR transection* OR 'sublobar resection' OR 'subpial transection'
8	Brain Stimulation	'brain depth stimulation'/de OR 'brain responsive neurostimulator'/de OR 'deep brain stimulator'/de OR 'nerve stimulation'/de OR 'nerve stimulator'/de OR 'vagus nerve stimulation'/de OR ('brain stimulat*' OR 'deep brain stimulat*' OR 'electric brain stimulat*' OR 'external trigeminal nerve stimulat*' OR 'responsive brain stimulat*' OR 'responsive neurostimulat*' OR 'vagus nerve stimulat*' OR stimulation OR stimulator*) OR ((brain OR 'deep brain' OR electric* OR responsive OR 'vagus nerve') NEAR/2 (electrostim* OR stimulat*)) OR neurostim*
9	Harms	anhidrosis/de OR 'adverse event'/de OR 'adverse drug reaction'/de OR 'behavior disorder'/de OR 'cognitive defect'/de OR 'developmental delay'/de OR 'developmental disorder'/de OR dystonia/de OR 'liver injury'/de OR 'loss of appetite'/de OR 'motor dysfunction'/de OR 'organ damage'/de OR 'patient harm'/de OR 'sleep disorder'/de OR sweating/de OR (advers* OR harm* OR 'side effect'):ab,ti,kw OR anhidrosis OR (appetite NEAR/3 (lose OR losing OR loss)) OR ((cognitiv* OR behavior* OR develop* OR motor OR movement OR neurodevelop*) NEAR/3 (effect* OR disorder* OR problem* OR symptom*)) OR ((cognitiv* OR develop* OR neurodevelopment*) NEAR/3 (delay* OR disorder* OR regress*)) OR dystonia OR hypohidrosis OR hypohydrosis OR (liver NEAR/3 (damag* OR injur*)) OR (miss* NEAR/3 milestone*) OR ((eat* OR perspir* OR sweat* OR sleep*) NEAR/3 (disorder* OR inability OR unable))
10	Parental Preferences	parent/de OR (parent* OR mother* OR father*):ab,ti,kw
11	Untreated Disease	'treatment refusal'/de OR ('not treated' OR 'no treatment' OR untreat*):ab,ti,kw OR (declin* OR forgo* OR 'not' OR no OR refus* OR withheld OR withhold*) NEXT/3 (treated OR treatment*)

12	Study Designs/ Publication Types	[english]/lim AND [1999-2020]/py NOT ([animals]/lim NOT [humans]/lim OR abstract:nc OR annual:nc OR 'book'/de OR (case NEXT/1 (report* OR stud*)):ti OR 'case report'/de OR 'case study'/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR diagnos*:ti OR 'diagnosis'/mj OR 'diagnostic accuracy'/mj OR 'diagnostic procedures'/mj OR 'diagnostic test'/mj OR 'diagnostic test accuracy study'/mj OR 'differential diagnosis'/mj OR 'editorial'/de OR editorial:it OR 'erratum'/de OR guideline*:ti OR letter:it OR 'note'/de OR note:it OR meeting:nc OR 'practice guideline'/de OR review/exp OR sessions:nc OR 'short survey'/de OR symposium:nc OR animal*:ti OR experimental:ti OR (vitro:ti NOT vivo:ti) OR canine:ti OR dog:ti OR dogs:ti OR mouse:ti OR mice:ti OR rabbit*:ti OR rat:ti OR rats:ti OR rodent*:ti OR sheep:ti OR swine:ti)
13	Combine sets/patient population	#1 OR #2 OR #3 OR #4
14	Combine sets (KQ1 Pharmacology)	#5 AND #12 AND #13
15	Combine sets (KQ2 Diet, Surgery, Brain Stimuation)	(#6 OR #7 OR #8) AND #12 AND #13
16	Combine sets (KQ3 Harms)	#9 AND #12 AND #13
17	Combine sets (CQ1 Parental Preferences)	((#5 OR #6 OR #7 OR #8 OR #9) AND #10) AND #12 AND #13
18	Combine sets (CQ2 Untreated/ Uncontrolled Epilepsy)	#11 AND #12 AND #13
19	Combine Sets All KQs	#14 OR #15 OR #16

20	Combine Sets All CQs	#17 OR #18
22	**ALL RESULTS**	#19 OR #20