

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

Minimizing Bias in AHRQ Evidence-based Practice Center Program Systematic Reviews

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NASEM Workshop: Sponsor Influence on Health Research
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Disclosures and Disclaimers

- No financial conflicts of interest to disclose.
- I am an employee of the Agency for Healthcare Research and Quality (AHRQ) in the U.S. Department of Health and Human Services (HHS).
- No statement in this presentation should be construed as an official position of AHRQ or HHS.
- I am also an Adjunct Professor of Medicine at Georgetown University School of Medicine and provide clinical care at MedStar Georgetown University Hospital.

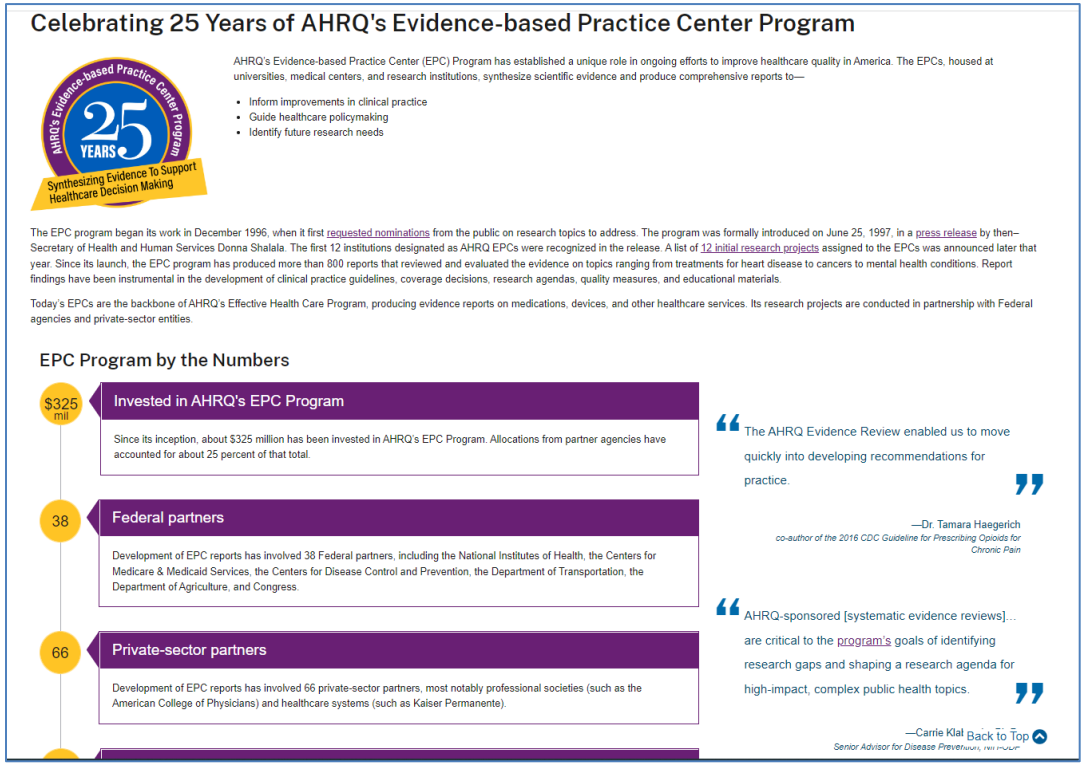
Agency for Healthcare Research and Quality (AHRQ) Mission Statement

- To produce evidence to make healthcare safer, higher quality, more accessible, equitable and affordable
- To work with HHS and other partners to make sure that the evidence is understood and used

www.ahrq.gov

AHRQ Evidence-based Practice Center (EPC) Program

- Established in 1997 (25th Anniversary!)
- Provides systematic reviews of published scientific evidence on range of health topics
  - Clinical
  - Healthcare delivery
- Invests in methods development for evidence reviews
- Contracts with 9 academic/research organizations in US to conduct work



Celebrating 25 Years of AHRQ's Evidence-based Practice Center Program

AHRQ's Evidence-based Practice Center Program 25 YEARS Synthesizing Evidence To Support Healthcare Decision Making

AHRQ's Evidence-based Practice Center (EPC) Program has established a unique role in ongoing efforts to improve healthcare quality in America. The EPCs, housed at universities, medical centers, and research institutions, synthesize scientific evidence and produce comprehensive reports to—

- Inform improvements in clinical practice
- Guide healthcare policymaking
- Identify future research needs

The EPC program began its work in December 1996, when it first requested nominations from the public on research topics to address. The program was formally introduced on June 25, 1997, in a press release by then–Secretary of Health and Human Services Donna Shalala. The first 12 institutions designated as AHRQ EPCs were recognized in the release. A list of 12 initial research projects assigned to the EPCs was announced later that year. Since its launch, the EPC program has produced more than 800 reports that reviewed and evaluated the evidence on topics ranging from treatments for heart disease to cancers to mental health conditions. Report findings have been instrumental in the development of clinical practice guidelines, coverage decisions, research agendas, quality measures, and educational materials.

Today's EPCs are the backbone of AHRQ's Effective Health Care Program, producing evidence reports on medications, devices, and other healthcare services. Its research projects are conducted in partnership with Federal agencies and private-sector entities.

EPC Program by the Numbers

$325 mil — Invested in AHRQ's EPC Program

Since its inception, about $325 million has been invested in AHRQ's EPC Program. Allocations from partner agencies have accounted for about 25 percent of that total.

"The AHRQ Evidence Review enabled us to move quickly into developing recommendations for practice."

—Dr. Tamara Haegerich, co-author of the 2016 CDC Guideline for Prescribing Opioids for Chronic Pain

38 — Federal partners

Development of EPC reports has involved 38 Federal partners, including the National Institutes of Health, the Centers for Medicare & Medicaid Services, the Centers for Disease Control and Prevention, the Department of Transportation, the Department of Agriculture, and Congress.

66 — Private-sector partners

Development of EPC reports has involved 66 private-sector partners, most notably professional societies (such as the American College of Physicians) and healthcare systems (such as Kaiser Permanente).

"AHRQ-sponsored [systematic evidence reviews]... are critical to the program's goals of identifying research gaps and shaping a research agenda for high-impact, complex public health topics."

—Carrie Klaf, Senior Advisor for Disease Prevention, HHS PCOR

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https://effectivehealthcare.ahrq.gov/about/epc-25-years

Current EPCs

- Brown University
- ECRI Institute - Penn Medicine
- Johns Hopkins University
- RTI International—University of North Carolina
- Mayo Clinic
- University of Minnesota
- Oregon Health and Science University
- Kaiser Permanente Research Affiliates
- University of Southern California - RAND

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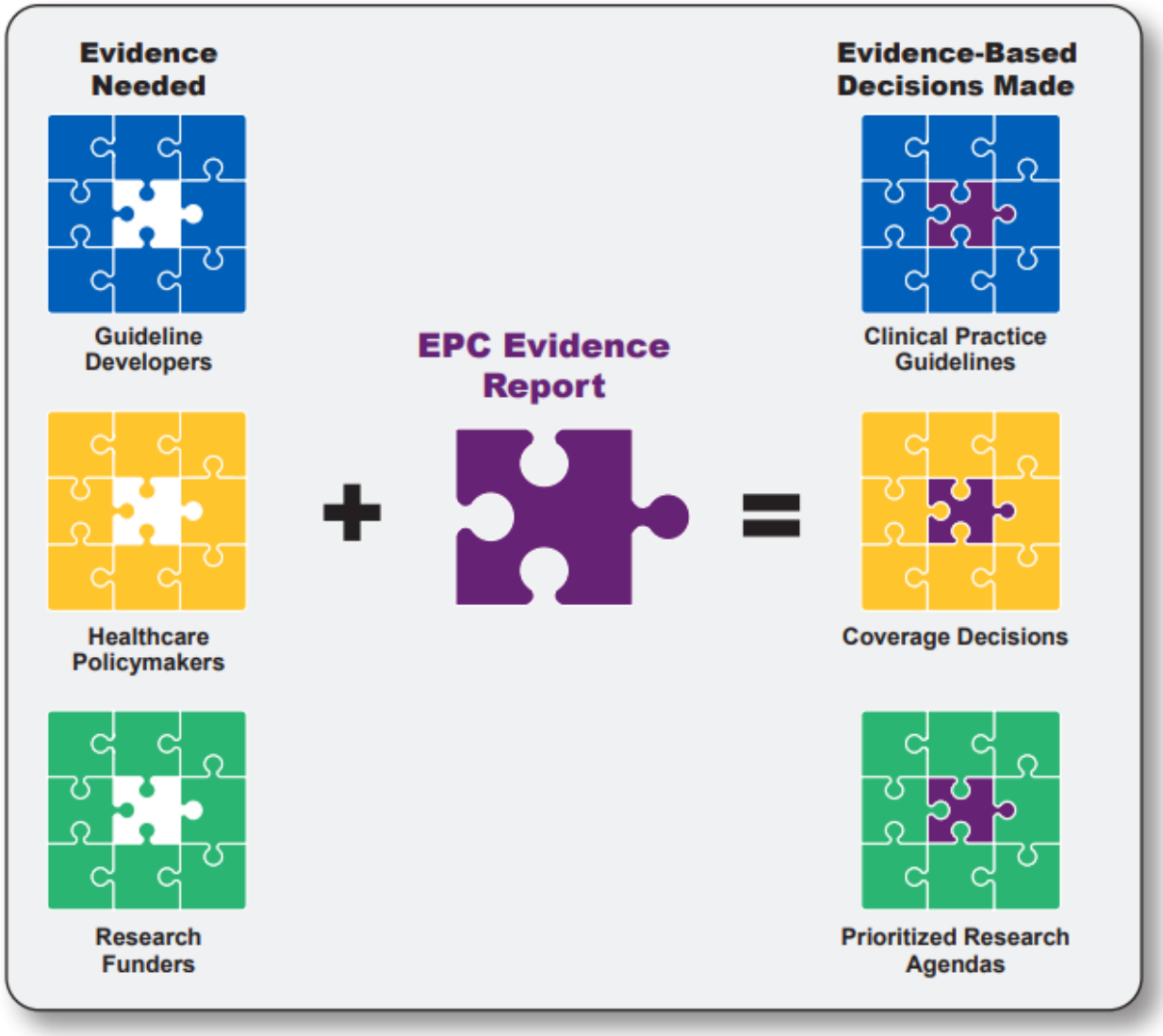
AHRQ EPC Program: Partnerships for Impact



U.S. Preventive Services TASK FORCE

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

ACP

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

UNITED STATES CONGRESS

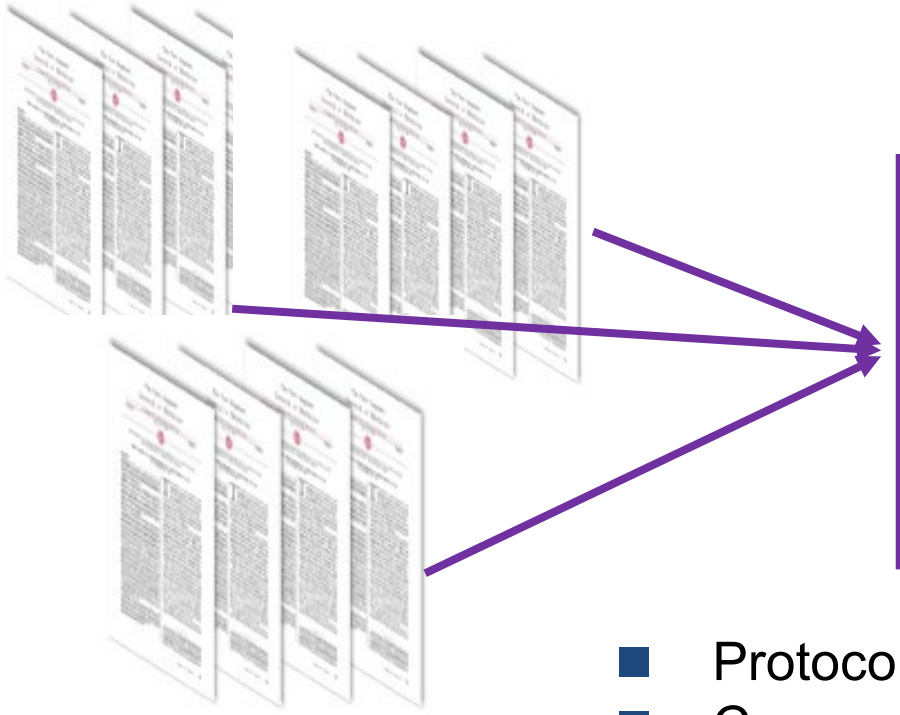
NIH

pcori

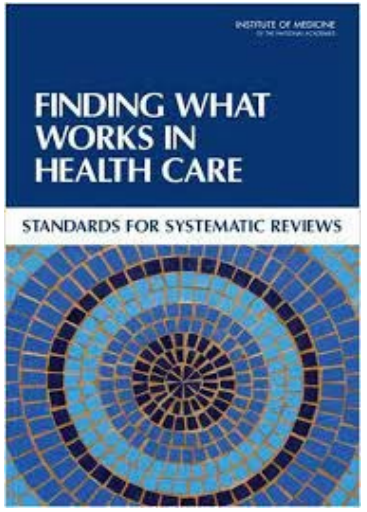
25 Years of Impact, by the Numbers

- >800 completed evidence reviews
- >100 unique partners (1/3rd Federal, 2/3rd Non-Federal)
- Informing approximately:
  - 200 US Preventive Services Task Force (USPSTF) prevention guidelines
  - 200 clinical practice guidelines issued by Federal and Society partners
  - 35 National Coverage Determinations by CMS
  - 40 NIH research prioritization meetings

What is an AHRQ EPC Systematic Review?

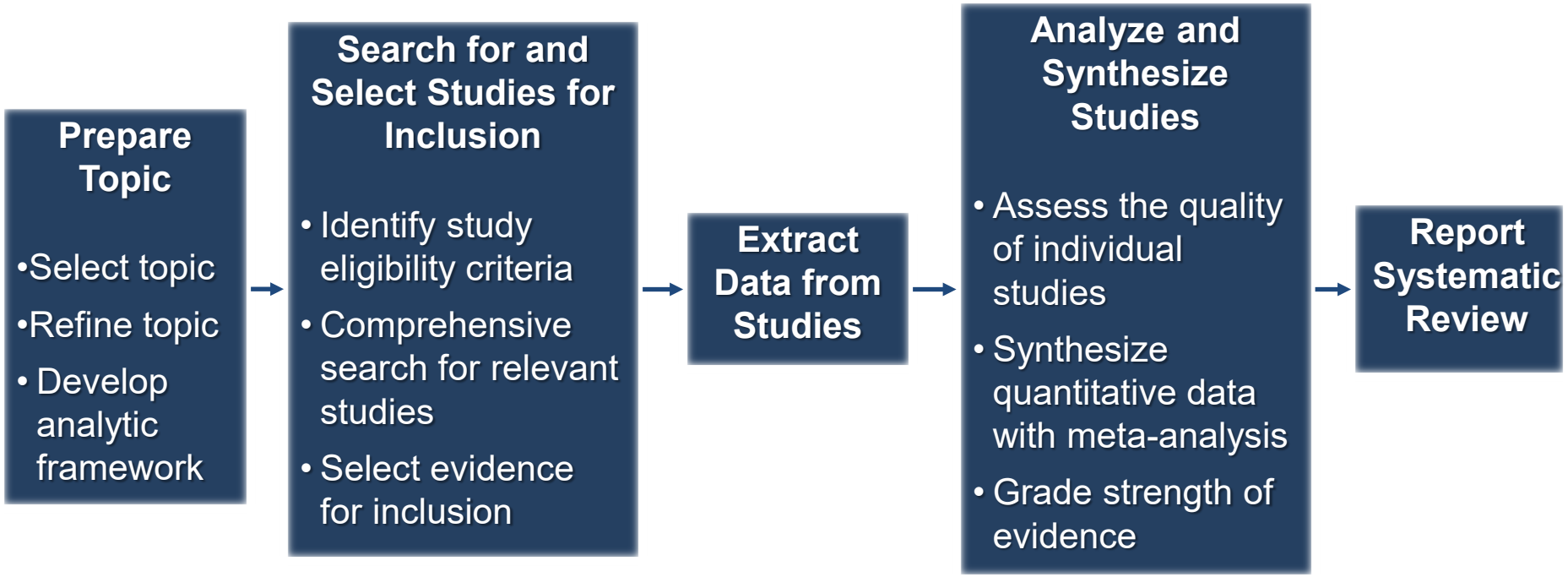


Summary of Overall Evidence to Address a Set of Key Questions



- Protocol-driven
- Comprehensive search of existing peer-reviewed studies
- Critical appraisal of each study identified
- Summarize findings for each key question across important outcomes, including benefits and harms

Systematic Review Process



Example: Management of Infantile Epilepsies

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Systematic Review | Oct 25, 2022

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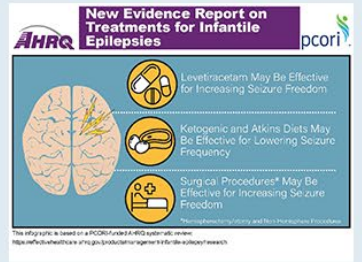
- Main Points
- Structured Abstract
- Visual Dashboard
- Report Snapshot
- Journal Citations
- Report Citation

Project Timeline

Management of Infantile Epilepsy

Jul 16, 2020	Topic Initiated
Feb 3, 2021	Research Protocol
Oct 25, 2022	**Systematic Review**



New Evidence Report on Treatments for Infantile Epilepsies (PDF, 759 KB)

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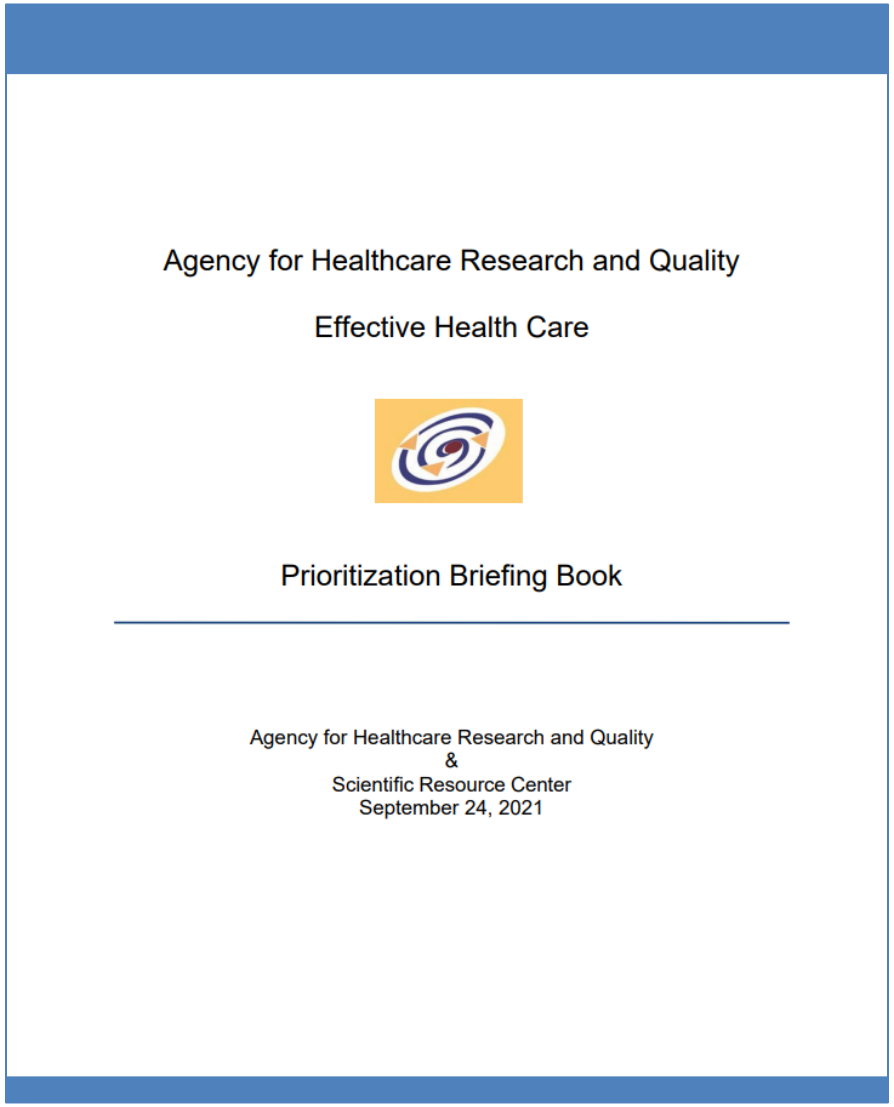
Partners: American Epilepsy Society, PCORI

Prioritize Topics to Address

- **Topic appropriate for review**
  - Related to healthcare
  - Available in the US
- **Important topic**
  - Significant disease burden
  - Vulnerable population
  - High public interest
  - High costs
- **Absence of duplication**
  - No recent reviews
- **Existing research**
  - Studies available
- **End user**
  - Identified partner
  - Amenable to using report to inform change


Agency for Healthcare Research and Quality

Effective Health Care

Prioritization Briefing Book

Agency for Healthcare Research and Quality
&
Scientific Resource Center
September 24, 2021

Scoping the Review

- **P**opulation (s):
  - Who is being evaluated?
  - Are relevant sub-populations examined? (elderly, adolescents, pregnant, underserved)
- **I**ntervention (s):
  - What is being evaluated?
- **C**omparator (s):
  - What is the intervention compared to?
- **O**utcomes:
  - What are the important outcomes for your topic?
  - Clinical versus surrogate outcomes? Patient-centered?

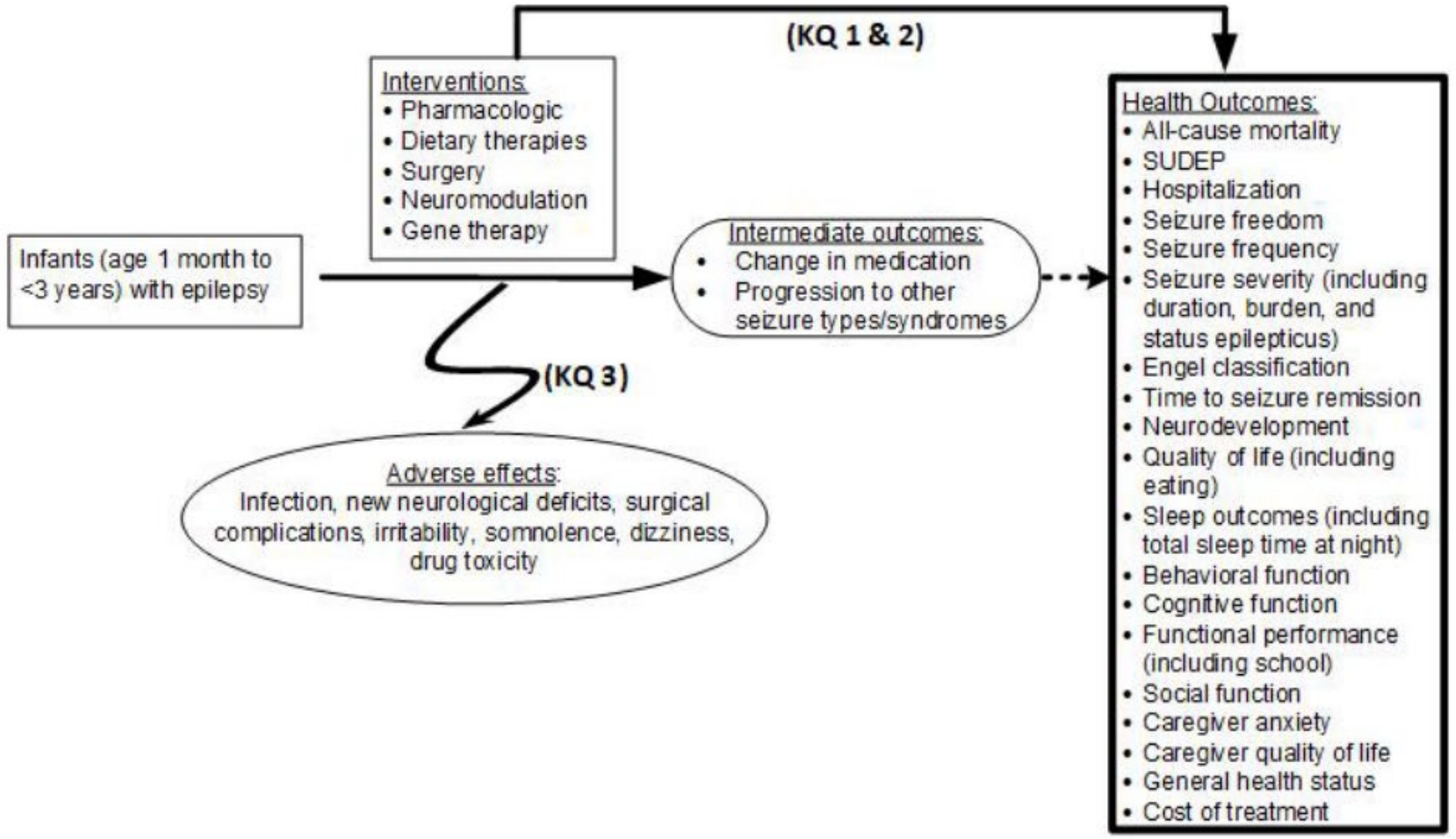
Experts Inform Scope of Review

- Pediatric neurologists
- Pediatric neurosurgeons
- Epilepsy Nurse Practitioner
- Dietician
- PhD (Epilepsy Research)
- Executive Director of Family Advocacy Foundation

- Experts must disclose financial COIs and any other relevant professional COI
- Because of their unique content expertise, those with potential conflicts may still be retained
- Aim to balance, manage, or mitigate potential COIs

Infantile Epilepsy Review

Figure 1. Analytic framework

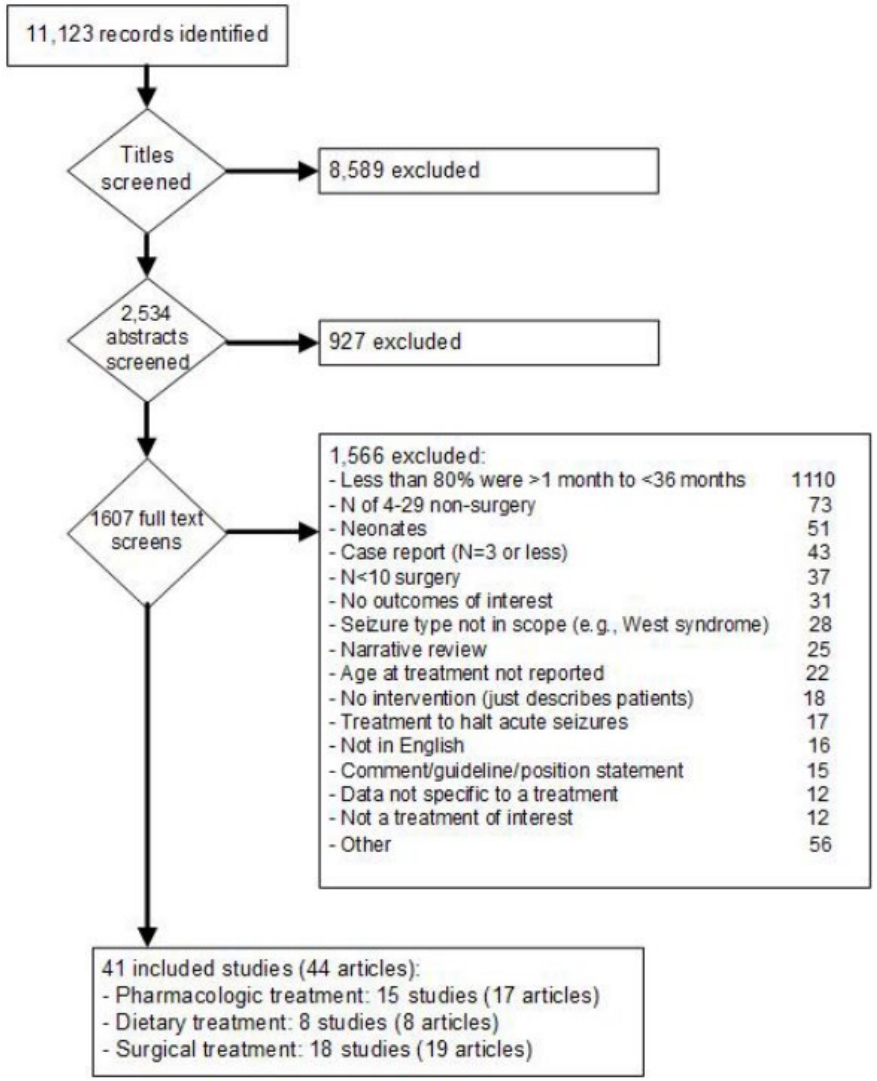


P	I	C	O	
Population	Intervention and Comparator		Intermediate Outcomes	Patient Centered Outcomes

Pharmacologic Treatments Examined

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

Study Flow Diagram



- Comprehensive search
- Multiple databases
- Two independent screeners
- Two independent data extractors

Study Risk of Bias (RoB) Assessment

- Use RoB assessment tools based on study designs
- For RCTs, we used:
  - Cochrane Risk of Bias 2 (ROB2) tool
- For non-randomized studies with control groups, we used:
  - Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool

Domains Assessed in RoB Tools

- How similar are test and control groups at baseline
- Adherence of groups to assigned intervention
- Completeness of outcome assessment in each study group
- Blinding of those prescribing and receiving interventions, and those evaluating outcomes

RoB Assessments Can Help Identify and Mitigate Bias Resulting from COIs

- **Are studies selecting specific designs and hypotheses?**
  - picking inferior comparison drugs and doses
- **Are studies selectively reporting outcomes?**
  - reporting select outcomes from multiple available endpoints
  - using composite endpoints without presenting data on individual endpoints

Example: RoB Table for RCTs

Table C-6. Pharmacologic intervention: Risk of bias of RCTs

Trial and Outcome	Generation Randomization	Allocation Concealment	Baseline Imbalance	Patient Blinded	Staff Blinded	Differential Ancillary Treatments	Adherence	Analytic approach to address departures from	Data On At Least 80% of those Enrolled	Differential Dropout <=15%	Standard Way To Measure The Outcome	Blinded Outcome Assessor	Bias In Selection Of Reported Results	Overall Risk of Bias
Liu et al. (2020)[1584] Seizure freedom	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	Low	**High**
Liu et al. (2020)[1584] Quality of life	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	Low	**High**
Novotny et al. (2010)[1594,1595] Adverse events	Low	Low	Low	Low	Low	SC	Low	Low	Low	Low	Low	Low	Low	**Low**
Manitpisitkul et al. (2013)[1596] Adverse events	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	High	Low	**Moderate**
Liu et al. (2020)[1584] Adverse events	SC	SC	SC	Low	SC	SC	SC	SC	Low	Low	Low	SC	SC	**High**
Piña-Garza et al. (2008)[1588,1589] Adverse events	SC	SC	SC	Low	Low	Low	SC	Low	Low	Low	Low	Low	Low	**Moderate**

We only rated risk of bias for studies for which we rated the strength of evidence (SOE). Other studies are discussed in the text.
SC = Some concerns

How to Use RoB Assessments

- Explore differences in results between higher and lower RoB studies
- Interpret impact of study RoB using sensitivity analysis
- Grade the strength of evidence

Determining the Strength of Evidence

Grade the **Strength of Evidence** for interventions across all studies by outcome, and consider factors such as:

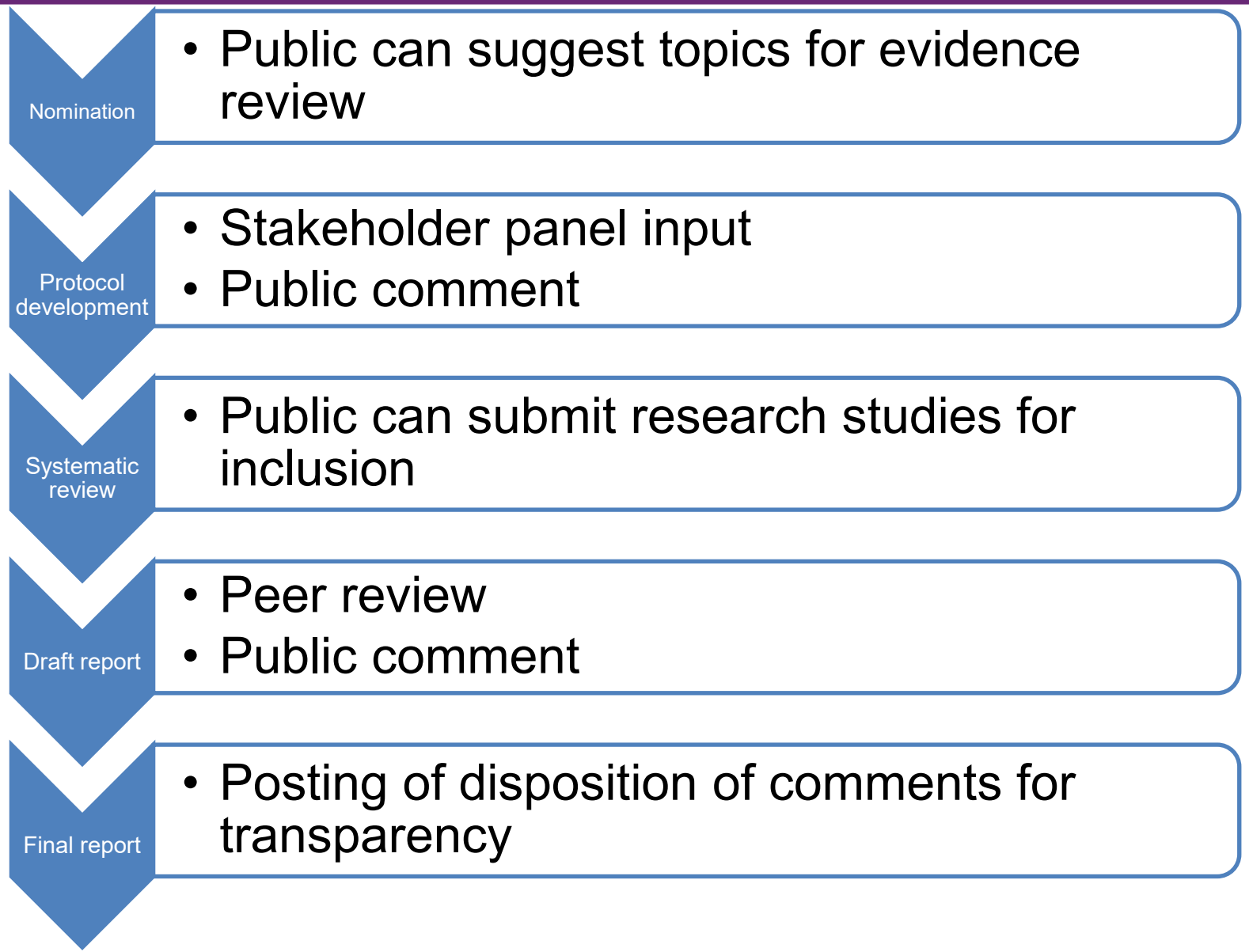
- Designs of studies informing the outcome
- RoB of studies informing the outcome
- Consistency of studies examining the outcome
- Precision of results
- Magnitude of effect

Example: Strength of Evidence Table

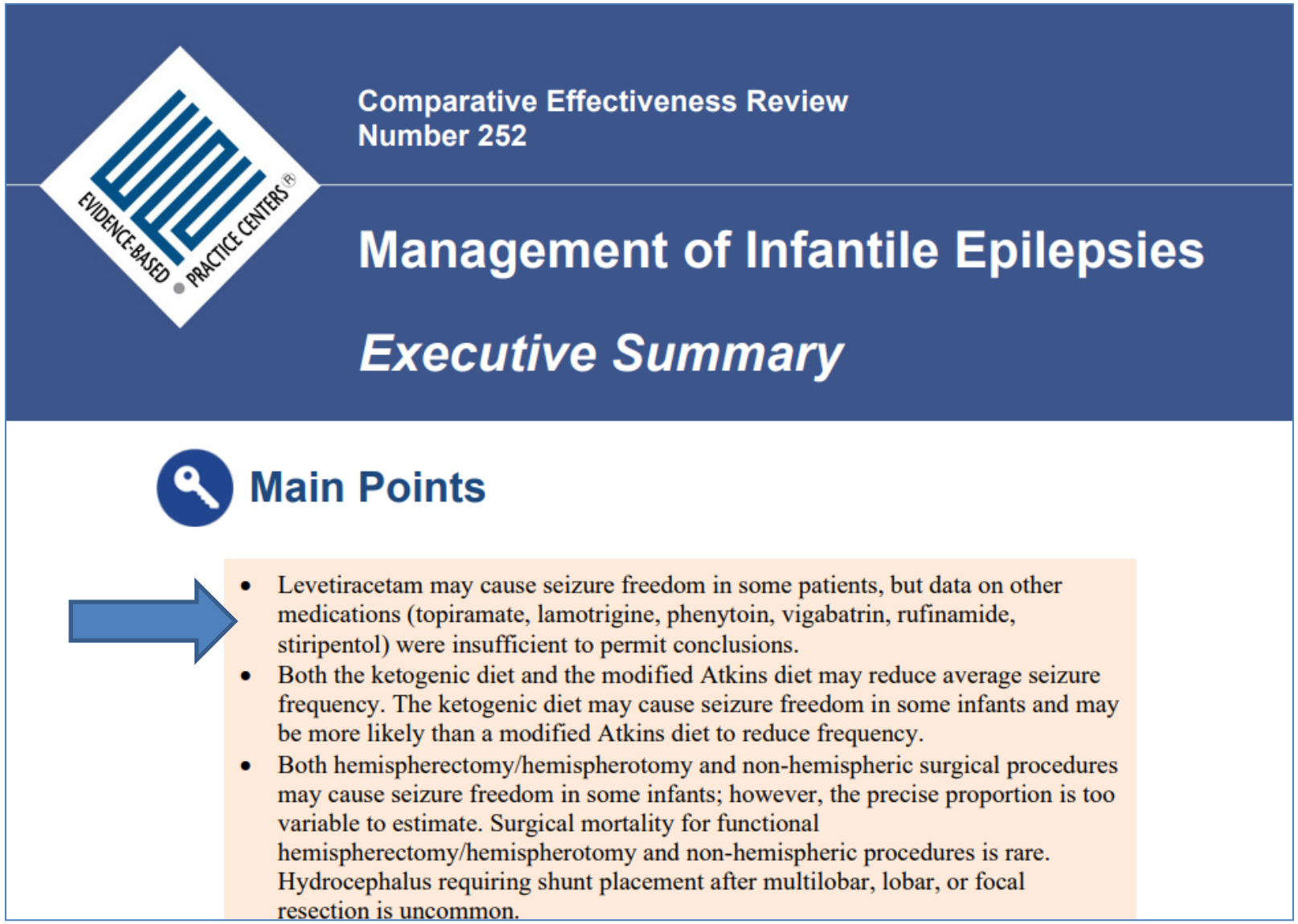
Table 3. Strength of evidence for Key Question 1

Treatment	Outcome	Study Findings	Risk of Bias	Directness	Consistency	Precision	Reporting Bias	Other Factors	Strength of Evidence	Conclusion
Levetiracetam (LEV)	Seizure freedom	One RCT[33] N=100 reported seizure freedom rates of 32% (16/50) with LEV+valproate vs 22% (11/50) with valproate alone (odds ratio 1.7, 95% CI 0.7 to 4.1) One pre/post study[34] reported 66% seizure freedom (61/92)	High	Direct	Consistent	Precise	None suspected	None	Low	Adding levetiracetam may cause seizure freedom in some infants
Levetiracetam (LEV)	Quality of life	One RCT[33] N=100 reported QOL scores of scores 84 with LEV+valproate vs 60 valproate alone (12 week follow-up) (statistically significant)	High	Direct	Unknown	Precise	None suspected	None	Insufficient	NA
Topiramate	Seizure freedom	One non-randomized comparative study[36] reported 59% seizure freedom (24/41) One pre/post study[37] reported 19% seizure freedom (11/58) One pre/post study[35] reported 8% seizure freedom (3/37)	High	Direct	Inconsistent	Imprecise	None suspected	None	Insufficient	NA
Topiramate vs carbamazepine	Seizure freedom	One non-randomized comparative study N=146:[36] topiramate 59% (24/41) vs carbamazepine 55% (58/105)	High	Direct	Unknown	Imprecise	None suspected	None	Insufficient	NA

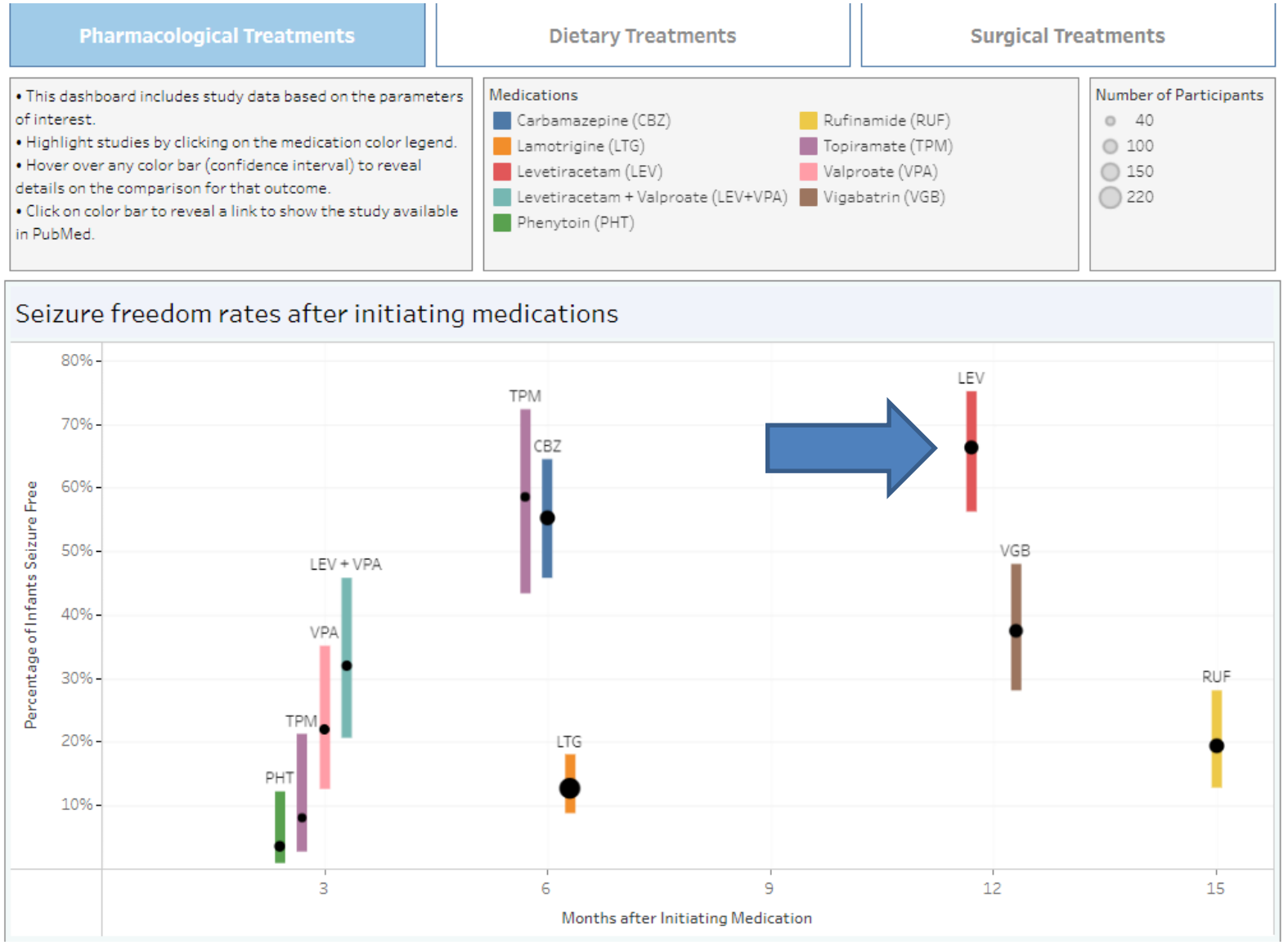
Stakeholder Engagement and Transparency Minimize Potential Bias



Executive Summary



Interactive Visual Dashboard



AHRQ EPC Methods Guide

Research Methods & Tools

Tools & Software

Education Resources

Research Methods & Tools

The Evidence-based Practice Center (EPC) Program has developed evidence synthesis guidance, tools, and education resources for those conducting and learning about research synthesis. Select a topic below to learn more.

EPC Methods Guide for Comparative Effectiveness Reviews

To improve transparency, consistency, and scientific rigor, the EPC Program has developed a Methods Guide for Comparative Effectiveness Reviews. It is continuously updated as a living document.

EPC Methods Guide for Medical Test Reviews

This guide complements the Methods Guide for Comparative Effectiveness Reviews, and is a practical resource for investigators in the EPC Program on preparing, conducting, and using systematic reviews of medical tests.

Tools & Software

Explore tools and software to support researchers and educators conducting systematic reviews.

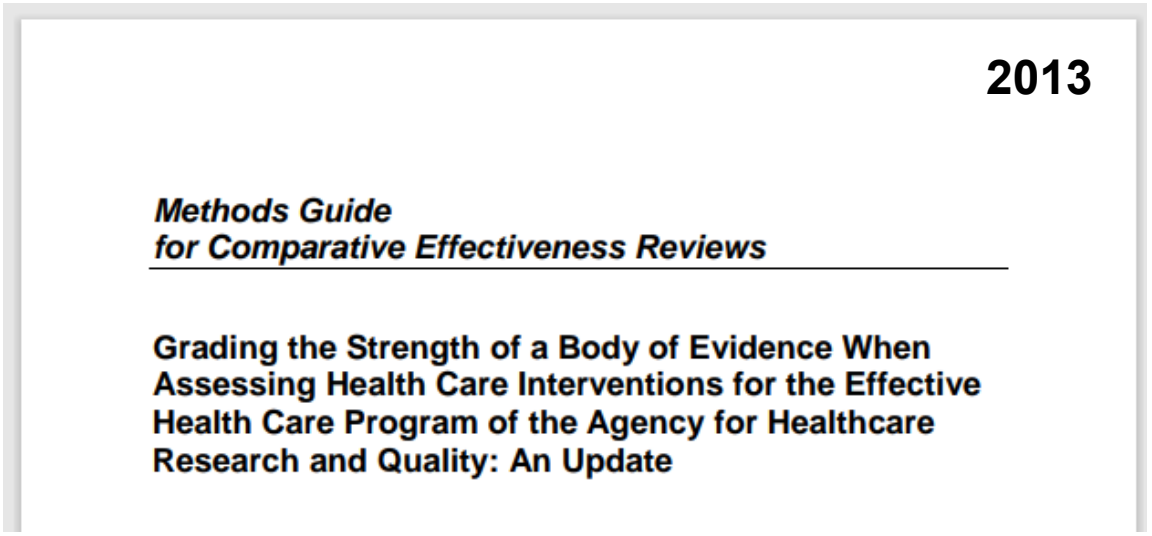
Education Resources

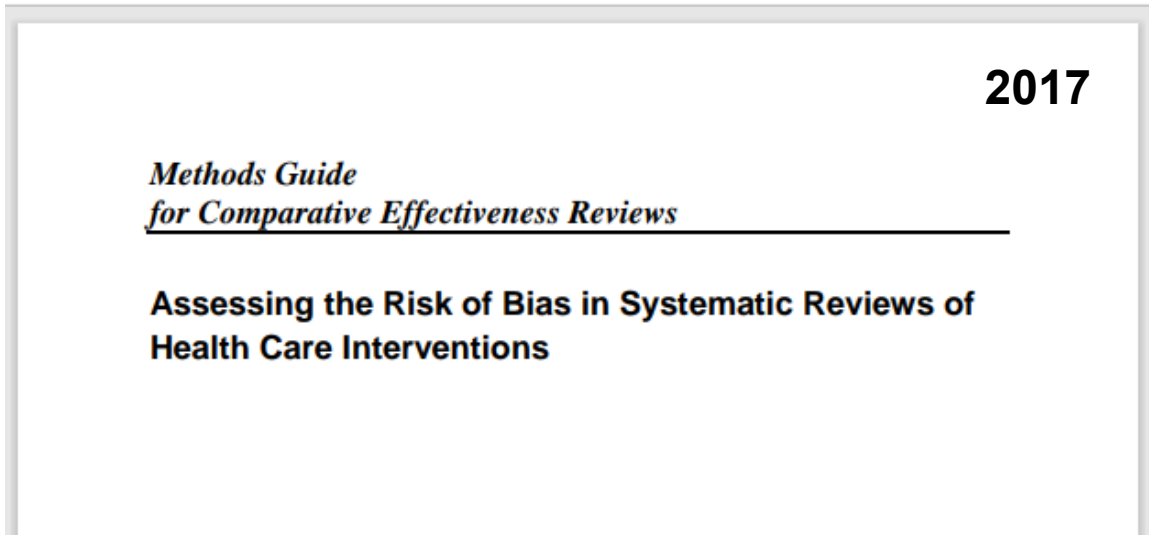
Explore education resources on systematic reviews, including slide presentations.

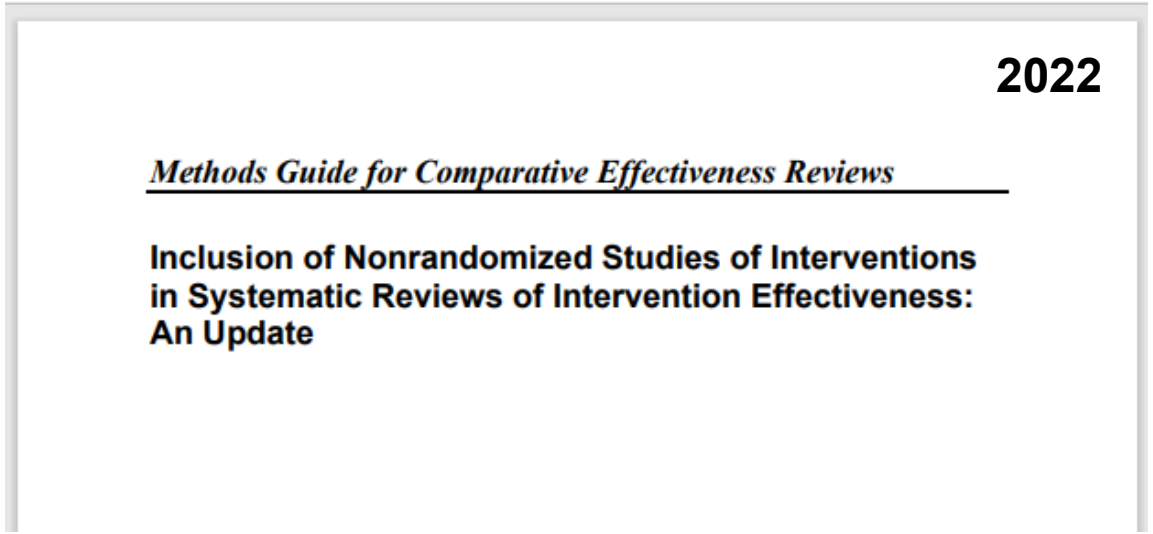
Methods Research

Search Methods Research Reports and White Papers from the EPC Program.

Relevant Methods Guide Chapters







Unique Characteristics of AHRQ EPC Reviews

Scientifically Rigorous	• EPC Methods Guide • Peer reviewed
Independent and Unbiased	• Conflicts of interest evaluation • Transparency and public comment
Stakeholder-Driven	• Identifying evidence needs • Provides ongoing input during review • Disseminating and Implementing reviews

EPC Program Goal: Improve health outcomes through partnership!

Evidence Review

-Guidelines
-Measures
-Policy

Practice Change

Further Research

Improved Health Outcomes

For More Information

- Craig Umscheid, MD, MS, Director, EPC Division
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  - https://effectivehealthcare.ahrq.gov/
- To sign up for notifications
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