S1: Summary of recommendations for developing Clinical Practice Guidelines

Minimum CPG development requirements (where resources are more limited) are bolded. When full resources are available, every recommendation should be considered to produce the highest quality CPG.

Component of CPG development	ILAE Recommendation	Document
Identifying topic and developing clinical research question	**Answerable clinical questions must be clearly stated and be developed using the PICO format (i.e., the population(s), intervention(s), comparator(s), and outcome(s) of interest must be specifically defined). The type of question (therapy, diagnosis, prognosis, etc.) should be identified at the outset.** **The objectives and scope of the CPG need to be explicitly stated. The objectives should include details about the potential impact on health and the potential benefits from the recommendations.** If the authors plan to seek ILAE endorsement of their CPG, and to publish it in *Epilepsia,* a protocol must be completed and submitted to the ILAE guideline advisory committee. The protocol template is available on the ILAE website and is also included in S3.	S3

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S1: Summary of recommendations for developing Clinical Practice Guidelines

Establish working group	**The target audience that will be implementing the CPG should be determined and explicitly stated, and should be represented on the CPG working group.** **The CPG working group should include around ten members, and at a minimum should be composed of:** **1. A member assigned by the ILAE executive to represents the ILAE as a stakeholder** **2. Experts in the clinical area of the guideline** **3. A member with expertise in CPG development methodologies (if none of the other members has such experience)** **4. A representative from the target audience (i.e. general practitioners)** **5. Representatives of other relevant professional group (s)** While not required, it is strongly recommended that a project manager and a patient representative be included. If representation from a patient is not feasible, the patient perspective should be sought through consultation with a patient, or the literature around patient perspectives should be included in the review.	

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S1: Summary of recommendations for developing Clinical Practice Guidelines

	Two thirds of the CPG working group members should be void of conflicts of interest and of representation from the pharmaceutical and medical device industry. **Each member of the CPG working group must complete an ILAE declaration of interests form (S4) prior to beginning work on that guideline.** **Declaration of interests should be made at each meeting and between meetings if new potential conflicts arise for any member of the CPG working group.** **All declarations of interest should be published with the guideline.**	S4
Reviewing the evidence	**Systematic review methodology, as per the PRISMA checklist (S5) should be used to synthesize the evidence.** **The search strategy should be done, at minimum, using Medline or PubMed, and EMBASE (S6).** If resources permit, a librarian with expertise in health research should assist with developing the search strategy. Additionally the search strategy should be run in other relevant databases, especially Cochrane Central and Cochrane database of Systematic Reviews, and grey literature sources. **A flow diagram of study selection (PRISMA flow diagram, S7) should be generated. The criteria for inclusion and exclusion of studies should be**	S5, S6, S7

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S1: Summary of recommendations for developing Clinical Practice Guidelines

	clearly stated. **Two independent reviewers should screen titles, abstracts and full text articles for eligibility criteria. Data should be abstracted independently by at least two trained data abstractors. A third reviewer should be sought to resolve disagreements at the full text screening phase and the data abstraction phase.** A meta-analysis should be conducted if possible and appropriate. The appropriate modeling method (i.e. fixed vs. random) should be chosen a priori. If heterogeneity is identified between studies, possible sources of heterogeneity should be discussed. An Egger's funnel plot should be generated to determine if publication bias is present. **The strengths and limitations of the current evidence should be discussed.**	
Evaluating the evidence	**The GRADE system should be used to evaluate the quality of the evidence, in conjunction with the criteria outlined in S8.** **The GRADE evidence profiles should be included in the CPG as an appendix.**	S8, S9
Formulating the recommendations	**The GRADE should be used to formulate CPG recommendations. Each recommendation should contain a grading of its strength (weak or strong).** **The criteria for each of the four factors that influence the strength of**	S10

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S1: Summary of recommendations for developing Clinical Practice Guidelines

	the recommendations should be clearly stated using S10. **The recommendations should be easy to identify (i.e. through the use of larger font, bold font, or headings).** **The recommendations should be clear and unambiguous, and should be formulated using the wording recommended by GRADE.** **Key recommendations should be accompanied by a discussion of other management options based on the four factors that impact the strength of the recommendations.**	
Peer review	**The CPG protocol (S3) should be reviewed by the ILAE guideline advisory committee or representatives from the ILAE executive prior to proceeding with the development of the full CPG.** **The first draft of the full CPG should be reviewed by the ILAE advisory committee or its representatives for approval. It should also be reviewed by the professional organization of the target users. Once this draft has been approved by the ILAE it should be posted on the ILAE website for public comments for a period of 30 days.** **A final draft will be submitted to *Epilepsia* for publication where it will undergo standard editorial and peer review.**	
Implementation, dissemination, and auditing	**Epilepsy-related CPGs should be freely disseminated through publication in *Epilepsia*, on the ILAE website, and communication to all chapter members electronically.**	

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S1: Summary of recommendations for developing Clinical Practice Guidelines

	Dissemination and implementation should be considered throughout the development process. Specifically, a stakeholder and/or target user should be included in the CPG working group, who can voice concerns about barriers to the implementation in clinical practice and provide feedback regarding possible facilitators. The potential barriers to implementation of the CPG, as identified by stakeholders and/or target users should be discussed in the final CPG. However, local organizations and ILAE chapters are best suited to carry out implementation strategies. Knowledge of the local context and availability of resources are essential to the successful implementation of CPGs. **The final draft of the CPG should be reviewed by members of the professional organization representing the target users, prior to being approved by the ILAE executive or its representative(s).** Suggestions for implementation and auditing should be included in the CPG. These should contain quality indicators or metrics to evaluate its impact on clinical care. While CPGs can help inform physicians about the evidence and its quality, and recommend a course of action, CPGs are not substitutes for the clinical judgement that is exercised during each clinical encounter.	
Updating and retiring	**A "review by" date should be associated with the CPG and should be based on the date that the systematic review was conducted.**	

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S1: Summary of recommendations for developing Clinical Practice Guidelines

	A systematic review of the evidence (using the same search strategy used to initial develop the CPG, unless new terminology has been developed) be conducted every two years to determine if a revision or update for the CPG is required in the case where new evidence is available that may significantly change the recommendations. If such evidence has not been published in the interim, the CPG authors may include a statement that the recommendations do not need to be modified based on this new evidence. If new evidence has become available a working group will need to be established to review the evidence and formulate revised recommendations (if warranted) based on the newly available evidence.	

Note: The original version of this supplement incorrectly referenced the associated supplemental material and has been replaced by this version.

S2: Clinical Practice Guideline development processes checklist

1. Topic selection & scoping of the CPG

- ☐ Complete ILAE clinical practice guideline development protocol
- ☐ Objective of the CPG is clearly stated and includes the potential impact of the CPG
- ☐ The clinical questions are outlined using the PICO format
- ☐ The population for whom the CPG is intended to address is clearly defined

2. Clinical practice guideline working group

- ☐ Establish a working group of 5-10 members with representation from:
  - ☐ An ILAE representative
  - ☐ Experts in the clinical area of the guideline
  - ☐ A member with expertise in CPG development methodologies
  - ☐ A representative from the target audience
  - ☐ Other relevant professional groups
- ☐ The patient perspective has been sought and/or included
- ☐ The target users have been defined and clearly stated
- ☐ The declaration of conflict of interest has been completed for each member of the CPG working group

3. Systematic review of the evidence

- ☐ The search strategy has been documented and includes the date that the search strategy was run
- ☐ PRISMA checklist has been completed for the systematic review of the evidence
- ☐ PRISMA flow diagram has been completed and includes the reason for exclusion for excluded full text articles
- ☐ A meta-analysis has been performed, if appropriate
- ☐ A forest plot has been generated
- ☐ Sources of heterogeneity have been reported
- ☐ Publication bias has been evaluated
- ☐ The strengths and limitations have been discussed

4. Evaluating the quality of the evidence

- ☐ The methods for evaluating the quality of the evidence have been described
- ☐ The GRADE was employed to evaluate the strength and quality of the evidence in conjunction with the criteria outline in Appendix I
- ☐ The GRADE evidence profiles have been included in the CPG

5. Formulating recommendations

- ☐ The methods for formulating the recommendations have been described
- ☐ The recommendations are easily identified
- ☐ The strength of the recommendation is included with the recommendation

S2: Clinical Practice Guideline development processes checklist

- ☐ Logic for rating the strength of the recommendation according to the four criteria (balance between desirable and undesirable effects, values and preferences, strength of the evidence, and resource use) has been documented using Appendix K
- ☐ The other possible treatment options are provided (as per Appendix K)

6. Peer review

- ☐ The CPG protocol (Appendix D) has been approved by the ILAE
- ☐ The CPG has been peer reviewed internally (ILAE) by experts, and this has been documented
- ☐ The approved CPG has been posted on the ILAE for public comments, and the comments and resulting modifications (if appropriate) have been documented
- ☐ The approved CPG has been submitted to *Epilepsia* for final peer review

7. Dissemination, implementation, and auditing

- ☐ The CPG has been disseminated in *Epilepsia*, on the ILAE website, and sent electronically to members of ILAE chapters
- ☐ The potential barriers to the implementation of the CPG have been discussed
- ☐ Auditing measures in the form of quality indicators or metrics have been proposed

8. Updating and retiring

- ☐ A "Review by" date has been added to the CPG. This date should be two years from the date that the systematic review was conducted.
- ☐ The methods for updating the CPG have been outlined.

S3: Clinical Practice Guideline Protocol

Proposed title:

Proposed authors:

Background

Description of the population and setting:

Why is this guideline needed (refer to guideline development process document for list of pertinent questions)?

Guideline details

Clinical question(s) to be addressed:

Population:

Intervention:

Comparator:

Outcome:

Aims and objectives of the guideline:

Target audience:

Guideline development working group

Suggested working group members:

Other collaborations/collaborators:

Please indicate if there any real, potential, or perceived conflicts of interest:

Resources

Please indicate what resources are available to the working group to develop this guideline:

S3: Clinical Practice Guideline Protocol

Timelines:

	Year															
Month																
Protocol approval																
Establish working group (1st mtg)																
Systematic Review																
Evidence Profiles (GRADE)																
Draft guideline																
ILAE review draft guideline																
Public comment of draft guideline																
External review																
Modification to guideline																
ILAE approval and endorsement of guideline																
Electronic publication																

S4: Conflict of Interest Form

Activity/Committee:
Name: Click here to enter text.
E-mail: Click here to enter text.
Date: Click here to enter a date.

The following questions address the significant financial interests that may concern yourself or the members of your immediate family (first degree).

Within the past 12 months, did you or your immediate family receive remuneration(s), or financial compensations from any commercial or non-profit (advocacy) entity? For a given entity, disclose only the activities of 500USD or more in monetary value AND when they contribute to an aggregated value superior or equal to 5000 USD.

Respond in Section 1 or Section 2 below, as applicable.

Section 1

I have no financial relationships to disclose. ☐

Section 2

Financial interest or relationship	***Self/Family Member** As a direct revenue, or as a contribution to your institutional salary(ies)	****Institution** As a contribution to your institutional activities	**If yes, name of the commercial or non-profit entity, and nature of the relationship**
Consulting fees	Choose an item.	Choose an item.	Click here to enter text.
Speaker honoraria	Choose an item.	Choose an item.	Click here to enter text.
Research support: grant or contract (commercial, governmental or advocacy entities)	Choose an item.	Choose an item.	Click here to enter text.
Salaries, or grants from commercial or advocacy entities	Choose an item.	Choose an item.	Click here to enter text.
Editor related income	Choose an item.	Choose an item.	Click here to enter text.
Shares, Stock options received as compensation	Choose an item.	Choose an item.	Click here to enter text.

S4: Conflict of Interest Form

Royalties, license fees, contractual rights	Choose an item.	Choose an item.	Click here to enter text.
*, ** Shares, Stock options held in a company whose business is related to medicine or involves research with you	Choose an item.	Choose an item.	Click here to enter text.
Other	Choose an item.	Choose an item.	Click here to enter text.

*Exclude mutual funds held by you or your family

** greater than five percent of the company or greater than $10,000 in value

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

S6: An example of a search terms related to the PICO for drug resistant epilepsy & search strategy

Search terms associated with the PICO question

Population Terms	
Epilepsy	1. Epilepsy (explode)
Drug resistant	1. Drug resistan* 2. Drug-resistan* 3. Refractor* 4. Pharmacoresistan* 5. Medication resistan* 6. Intract*
Intervention & Comparator Terms	
	1. Carbamazepine 2. Phenytoin 3. Valproic acid 4. Valpro* 5. Phenobarbital 6. Levetiracetam 7. Lamotrigine 8. Topiramate
Outcome Terms	
Unrestricted	
Study Design	
Unrestricted	

Search Strategy

Database	**Search terms**
Medline (OVID)	1 drug resistan*.mp. 2 drug resistan*.tw. 3 drug-resistan*.mp. 4 drug-resistan*.tw. 5 medication resistan*.mp. 6 medication resistan*.tw. 7 refractor*.mp. 8 refractor*.tw.

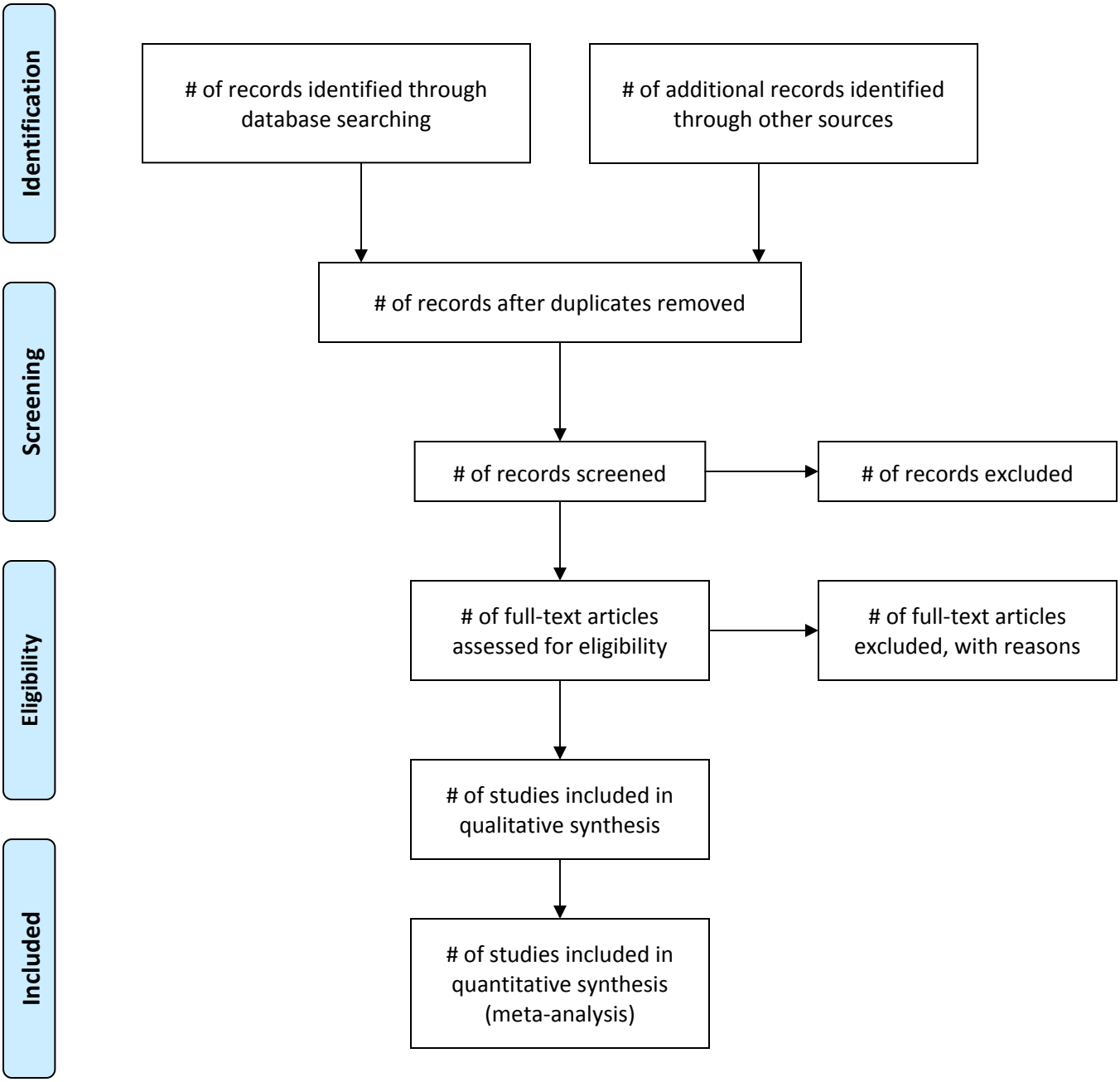
S6: An example of a search terms related to the PICO for drug resistant epilepsy & search strategy

	9 pharmacoresist*.mp. 10 pharmacoresist*.tw. 11 intractable.mp. 12 intractable.tw. 13 Carbamazepine.mp. or exp Carbamazepine/ 14 Carbamazepine.tw. 15 Phenytoin.mp. or exp Phenytoin/ 16 Phenytoin.tw. 17 valproic acid.mp. or exp Valproic Acid/ 18 valproic acid.tw. 19 valpro*.tw. 20 phenobarbital.mp. or exp Phenobarbital/ 21 phenobarbital.tw. 22 levetiracetam.mp. 23 levetiracetam.tw. 24 lamotrigine.mp. 25 lamotrigine.tw. 26 topiramate.mp. 27 topiramate.tw. 28 exp Epilepsy/ or epilepsy.mp. 29 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 30 13 or 14 or 15 or 16 or 17 or 18 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 31 28 and 29 and 30 32 limit 31 to animals 33 limit 32 to (animals and humans) 34 32 not 33 35 31 not 34
Embase (OVID)	1 drug resistan*.tw. 2 drug-resistan*.tw. 3 medication resistan*.tw. 4 refractor*.tw. 5 pharmacoresist*.tw. 6 intractable.tw. 7 Carbamazepine/ 8 Carbamazepine.tw. 9 Phenytoin/

S6: An example of a search terms related to the PICO for drug resistant epilepsy & search strategy

	10 Phenytoin.tw. 11 Valproic Acid/ 12 valproic acid.tw. 13 valpro*.tw. 14 Phenobarbital/ 15 phenobarbital.tw. 16 levetiracetam.tw. 17 lamotrigine.tw. 18 topiramate.tw. 19 Epilepsy/ 20 epilepsy.tw. 21 1 or 2 or 3 or 4 or 5 or 6 22 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15 or 16 or 17 or 18 23 19 or 20 24 21 and 22 and 23 25 limit 24 to animal studies 26 limit 25 to (animal and human) 27 25 not 26 28 24 not 27 29 limit 28 to embase

PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

S8: Factors that decrease the quality of evidence for studies of therapeutic or diagnostic tests

Factor	Explanation for therapeutic studies	Explanation for diagnostic studies
Study Design	Randomized controlled trials = High Observational studies = Low	Cross-sectional or cohort studies with diagnostic uncertainty and direct comparison of test results with reference standard = High
Risk of Bias Limitation in study design and execution. Risk of bias lowers our confidence in the estimate of effect in the study.	Three criteria should be considered: 1. Trials are described as randomized 2. Outcome assessment is described as masked 3. Dropout rate (both arms) is below or equal to 30% and are distributed similarly between arms Downgrade the quality of the evidence if: ***Serious risk of bias*** = one or more of the three criteria is not met in 10-30% of the studies included in the systematic review (downgraded by 1). ***Very serious risk of bias*** = One or more of the three criteria is not met in more than 30% of studies included in the systematic review (downgraded by 2).	1. Representativeness of the population that was intended to be sampled. 2. Independent comparison with the best alternative test strategy. 3. All enrolled patients should receive the new test and the best alternative test. 4. Diagnostic uncertainty should be given. 5. Is the reference standard likely to correctly classify the target condition?
Indirectness Patient population, intervention/diagnostic test, comparison, and indirect comparisons of tests	Criteria to be considered: 1. Population 2. Interventions and comparator used 3. Outcome measures (e.g. surrogate outcomes) Downgrade the quality of the evidence if: ***Serious doubts about directness*** = the question being addressed by the guideline development committee is different from available evidence in the study with regards to population,	1. Downgrade evidence if important differences between populations studied and population of interest. 2. Downgrade evidence if important differences between the tests studied and the diagnostic expertise of those applying them in the studies, compared to the setting of interest. 3. Downgrade evidence if the tests being

S8: Factors that decrease the quality of evidence for studies of therapeutic or diagnostic tests

	intervention, comparator, outcome, and those that will be delivering the intervention (downgrade by 1). ***Very serious doubts about directness*** = the question being addressed by the guideline development committee is markedly different from available evidence in the study with regards to population, intervention, comparator, outcome, and those that will be delivering the intervention (downgrade by 2).	compared are each compared to a reference (gold) standard in different studies and not directly compared in the same studies. *Accuracy studies typically provide low quality of evidence for guideline development due to indirectness of the outcomes.
Inconsistency Heterogeneity between individual study results. When heterogeneity is present without discussion around a possible cause, confidence in the estimate of effect is compromised.	Criteria to be considered: 1. Visual investigation of forest plots 2. Statistical test of heterogeneity (I^2) Downgrade the quality of the evidence if: ***Serious inconsistency*** = visual investigation of forest plots and a statistical test of heterogeneity indicates some degree of heterogeneity (I^2=50%-70%; downgrade by 1). ***Very serious inconsistency*** = visual investigation of forest plots and a statistical test of heterogeneity indicates high degree of heterogeneity (I^2 > 75%; downgrade by 2).	1. Downgrade evidence if, for accuracy studies, unexplained inconsistency in sensitivity, specificity or likelihood ratios.
Imprecision Precision refers to the statistical precision around the estimate of effect.	Criteria to be considered: 1. Sample size 2. Confidence intervals Downgrade the quality of the evidence if: ***Serious imprecision*** = the number of individuals included in the study is low (100-200 for both arms) or the 95% confidence	1. Downgrade evidence if individual studies have wide confidence intervals for the estimates of test accuracy, or true and false positive and negative rates.

S8: Factors that decrease the quality of evidence for studies of therapeutic or diagnostic tests

	interval includes no effect and appreciable benefit or harm (downgrade by 1). ***Very serious imprecision*** = the number of individuals included in the study is very low (less than 100 for both arms) or the 95% confidence interval includes no effect and appreciable benefit or harm (downgrade by 2). * For guideline panels, the decision to downgrade the quality of evidence for imprecision is dependent on the threshold that represents the basis for a management decision and consideration of the trade-off between desirable and undesirable consequences. Determining the acceptable threshold inevitably involves judgement that must be made explicit.	
Publication bias Over or underestimates the benefit or harm due to the lack of publications. Publication bias often results in missing small studies that show no effect.	Criteria to be considered: 1. Visual inspection of the funnel plot Downgrade the quality of the evidence if: ***Serious publication bias*** = graphical inspection of the funnel plot suggests asymmetry and may impact the summary estimate (downgrade by 1). ***Very serious publication bias*** = graphical inspection of the funnel plot suggests asymmetry and may substantial impact the summary estimate (downgrade by 2).	1. Downgrade evidence if a high risk of publication bias is present.

*Table adapted from the GRADE handbook available in the help section of GRADEpro or at: http://www.guidelinedevelopment.org/handbook/ and the WHO guideline development handbook

S9: Example of a GRADE evidence profile generated using GRADE Pro

Question: Should Topiramate vs. placebo be used in people of all ages with convulsive partial epilepsy?
Bibliography (systematic reviews): Pulman (2014)

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Topiramate	placebo	Relative (95% CI)	Absolute (95% CI)		
Efficacy (assessed with: 50% reduction in seizures)												
11	randomised trials	serious [1]	not serious	not serious	not serious	publication bias strongly suspected strong association dose response gradient	403/899 (44.8%)	73/502 (14.5%) 0%	**RR 2.97** (2.38 to 3.72)	0 fewer per 1000 (from 0 fewer to 0 fewer) 0 fewer per 1000 (from 0 fewer to 0 fewer)	HIGH	CRITICAL
Efficacy (seizure freedom)												
5	randomised trials	serious [1,2]	not serious	not serious	serious [2]	publication bias strongly suspected strong association dose response gradient [1]	23/356 (6.5%)	5/277 (1.8%)	**RR 3.41** (1.37 to 8.51)	44 more per 1000 (from 7 more to 136 more)	MODERATE	CRITICAL
Treatment acceptability (dropouts)												
10	randomised trials	serious [1]	not serious	not serious	serious [2]	publication bias strongly suspected strong association dose response gradient [1]	136/853 (15.9%)	29/462 (6.3%)	**RR 2.44** (1.64 to 3.62)	90 more per 1000 (from 40 more to 164 more)	MODERATE	IMPORTANT

MD – mean difference, RR – relative risk

1. details of outcome assessment blinding not adequately provided, dropout rate less than 30% but not similarly distributed between treatment arms
2. 95% confidence intervals include no effect and appreciable harm

S10: Example of an evidence to recommendation profile

Linking evidence to recommendation (see bottom of document for example)

Benefits	
Harms	
Summary of the quality of evidence	

Value and preferences	
In favour	
Against	
Uncertainty or variability?	

Feasibility/ Resource use	
Uncertainty or variability?	

S10: Example of an evidence to recommendation profile

Recommendation

Notes and discussion of other treatment options

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	☐ High ☐ Moderate ☐ Low ☐ Very low
Balance of benefits versus harms	☐ Benefits clearly outweigh harms ☐ Benefits and harms are balanced ☐ Potential harms clearly outweigh potential benefits

S10: Example of an evidence to recommendation profile

Values and preferences	☐ No major variability ☐ Major variability
Resource use	☐ Less resource-intensive ☐ More resource-intensive
Strength	☐ Weak ☐ Strong

The following example and others can be found at http://www.who.int/mental_health/mhgap/evidence/epilepsy/en/

Benefits	Lamotrigine, levetiracetam, and topiramate are superior to placebo as add-on therapy in controlling seizures in patients of all ages with drug resistant convulsive epilepsy. No systematic reviews of RCTs were found examining the efficacy of carbamazepine, phenobarbital, phenytoin, or valproic acid as add-on therapy in controlling seizures in patients of all ages with drug resistant convulsive epilepsy. No systematic reviews of RCTs were found examining the head-to-head efficacy of any of the antiseizure medications of interest for patients with drug resistant convulsive epilepsy. It is considered unethical to compare the efficacy of antiseizure medications against placebo alone in patients with established epilepsy, whether drug resistant or not since antiseizure medications have been found to decrease morbidity and premature mortality.

S10: Example of an evidence to recommendation profile

Harms	All antiseizure medications are associated with adverse effects. However, lamotrigine and levetiracetam had comparable withdrawal rates to placebo in patients of all ages with drug resistant convulsive epilepsy. Topiramate had higher withdrawal rates than placebo in patients of all ages with drug resistant convulsive epilepsy based on one systematic review. One randomized trial found a higher dropouts due to adverse events compared to valproic acid.
Summary of the quality of evidence	The balance of benefit versus harms is in favour of treatment of children and adults with drug resistant convulsive epilepsy. However, for critical outcomes, the quality of the evidence is low to high. For important outcomes, the quality of the evidence ranged from very low to moderate.

Value and preferences	
In favour	Most people would favour treatment over placebo to reduce their seizure frequency and as a result reduce the morbidity and mortality associated with ongoing seizures.
Against	All antiseizure medications are associated with a risk of medication withdrawal (usually due to adverse events) although the benefits outweigh the risks in most studies.
Uncertainty or variability?	Despite the fact that antiseizure medications are associated with some adverse events, most people with drug resistant convulsive epilepsy would choose to be on these medications to decrease the risk of morbidity and mortality.

S10: Example of an evidence to recommendation profile

Feasibility (including resource use considerations)	Carbamazepine, phenytoin, phenobarbital and valproic acid are included in the WHO list of essential medicines. However, there is a paucity of research examining the effect of these medications as add-on therapy in patients with drug resistant convulsive epilepsy. Although the newer antiseizure medications (levetiracetam, lamotrigine and topiramate) are not on the WHO list of essential medicines and are more costly than the older antiseizure medications, there is evidence to support their use as add-on therapy in patients with drug resistant convulsive epilepsy.
Uncertainty or variability?	Because these medications are not on the WHO list of essential medicines, this may represent a barrier to use in some countries.

Draft recommendation for consideration by the guideline panel

Draft recommendation

The newer antiseizure medications (lamotrigine, levetiracetam and topiramate) included in this evidence profile should be considered as add-on therapy in patients with drug resistant convulsive epilepsy.
Strength of the recommendation:

The essential antiseizure medications (carbamazepine, phenobarbital, phenytoin, and valproic acid may be of benefit as add-on therapy in patients with drug resistant convulsive epilepsy.

Remarks

Limitations: There were no head-to-head studies comparing the efficacy of the essential antiseizure medications and the newer antiseizure medications of interest against each other for adults and children with drug resistant convulsive epilepsy.

S10: Example of an evidence to recommendation profile

The majority of the studies included in the systematic reviews defined drug resistant epilepsy as failure of one or greater antiseizure medications which is not congruent with the currently accepted definition of drug resistant epilepsy. Had the new definition been adopted for this guideline it would have excluded many or all of the studies examining the efficacy and safety of the essential medications and the newer antiseizure medications examined. New studies using the new definition of drug resistant epilepsy as inclusion criteria are needed.

Note: Medication selection should also be appropriate based on the epilepsy syndrome as some antiseizure medications can worsen generalized convulsive seizures (e.g. carbamazepine, phenytoin and phenobarbital should be avoided in patients with myoclonic epilepsy) based on prior studies (not included in this analysis). Patients' comorbidites and childbearing potential also have to be considered when recommending a newer antiseizure medication in those with drug resistant convulsive epilepsy as some AEDs are associated with a higher risk of teratogenicity than other, or could worsen comorbid conditions (e.g. depression, obesity, etc.).

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	☐ High ☒ Moderate ☐ Low ☐ Very low
Balance of benefits versus harms	☒ Benefits clearly outweigh harms ☐ Benefits and harms are balanced ☐ Potential harms clearly outweigh potential benefits

S10: Example of an evidence to recommendation profile

Values and preferences	☒ No major variability ☐ Major variability
Resource use	☒ Less resource-intensive ☐ More resource-intensive
Strength	

S11: Useful links and resources

Systematic Review

Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) webpage: http://www.prisma-statement.org/

Cochrane handbook: http://handbook.cochrane.org

Search terms

http://resourcecenter.ovid.com/site/help/documentation/ospa/en/syntax.htm

Statistical software for meta-analysis

http://tech.cochrane.org/revman

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Main GRADE webpage: http://www.gradeworkinggroup.org/

GRADE handbook: http://www.guidelinedevelopment.org/handbook/

GRADE online software: www.guidelinedevelopment.org

GRADE learning modules: http://cebgrade.mcmaster.ca/aboutgrade.html

Example of recommendations (evidence profiles) developed using GRADE

http://www.who.int/mental_health/mhgap/evidence/epilepsy/en/

http://www.who.int/mental_health/mhgap/evidence/resource/epilepsy_q7.pdf