AMERICAN EPILEPSY SOCIETY

AES Clinical Practice Guideline Development Manual

Prepared by

David Gloss

2016-2019 Guideline and Assessment Committee Chair

135 S. LaSalle Street
Suite 2850
Chicago, IL 60603

Tel: 312.883.3800
info@asenet.org

American Epilepsy Society
Executive Office
135 S. LaSalle Street
Suite 2850
Chicago, IL 60603
Tel: 312.883.3800
Fax: 312.896.5784
Email: info@aesnet.org
www.aesnet.org

ACKNOWLEDGMENTS

Thanks to Gary Gronseth, Melissa Armstrong, Tamara Pringsheim, Cynthia Harden, Steve Messe, Sonja Potrebic, and Tom Getchius for allowing the American Academy of Neurology (AAN) manual to be used as the basis for the American Epilepsy Society (AES) manual. Thanks also to the 2015-2016 AES Guidelines and Assessment Committee members, especially Barbara Dworetzky and Nathalie Jette, for reviewing the manual draft and pointing out areas for clarification.

AES Clinical Practice Guideline Development Manual, 2020 Ed. Chicago, IL: American Epilepsy Society.
© 2020 American Epilepsy Society.

© 2020 American Epilepsy Society. All Rights Reserved. Adapted with permission from the American Academy of Neurology Institute

Table of Contents

Preface

The purpose of the *AES Clinical Practice Guideline Development Manual* is to create a transparent process so valid and credible guidelines can be developed by the AES. To a great extent, the manual is based on the 2011 American Academy of Neurology (AAN) guideline process manual[1] and the 2015 AAN amendments to the manual.[2]

Many sources of guidance were used in creating this manual.[1-18] When there was contradictory information, the manual generally follows the Institute of Medicine report, *Clinical Practice Guidelines We Can Trust*.[3]

Introduction to Evidence-Based Medicine

Evidence-based medicine (EBM) is a method for answering clinical questions by integrating the information from the best available research evidence with clinical expertise. There are three main approaches to answering questions using evidence-based medicine.

The first approach is to set a minimum bar, such as published studies that use a randomized controlled trial (RCT) research design. Relevant published studies are located and form the basis of the guideline. All other evidence would not be included in the guideline. The included studies are then individually classified on risk of bias and rereviewed as a group by using a system such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE). This approach has the advantage of limiting the review to the evidence with the lowest risk of bias but does not consider other forms of published data.

The second approach is to create a rating system for published studies and base the answers to the clinical questions on the highest level of evidence. This system can rate the papers based on risk of bias, so the assessment of bias is incorporated into the system of grading. This has both advantages and disadvantages compared with the first approach. The advantage is that weaker recommendations can be crafted when only weaker evidence is available. The disadvantage is that finding and rating the papers is labor intensive.

The third approach, the basis for some consensus-based clinical practice guidelines, is to find all the available evidence but not rate the evidence.

AES guideline development uses the second approach.

AES Guideline Development Process

AES guidelines are produced in a stepwise manner, and the steps are broadly outlined and described here. A summary of the steps can be found in Appendix One.

Step One: Nominate and approve topic

Step Two: Form the Work Group

Step Three: Disclose and review potential conflicts of interest

Step Four: Develop the protocol

> The basis of the guideline and core of the proposal are clinical questions written using a logical format that frames the questions, supports comprehensive literature searches, and enables focused answers. The protocol also defines inclusion and exclusion criteria and defines outcomes.

Step Five: Approve the protocol

Step Six: Find relevant literature

> Systematic literature searches will be conducted based on the structured clinical questions.

Step Seven: Screen literature search results

> Studies will be screened in two phases, abstract screening and full text screening, according to specified inclusion and exclusion criteria.

Step Eight: Classify evidence and conduct modified GRADE process

> Evidence in individual studies selected will be classified according to level of evidence and perceived risk of bias, evidence will be synthesized, and synthesis may involve performing a meta-analysis. The risk of bias will then be evaluated a second time for groups of papers and considering additional criteria than those used during the prior individual paper classification.

Step Nine: Write draft recommendations and vet via modified Delphi process

> Actionable recommendations will be crafted. Suggestions will then be made for future research to address any gaps in knowledge uncovered in the process of creating the guideline.

Step Ten: Write the draft guideline

> A draft of the guideline is written, after which it is carefully reviewed in a review process that consists of several steps.

Step Eleven: Review and approval processes

Step Twelve: Implementation and Dissemination

Step Thirteen: Updates

This manual describes two types of products. The first is a Practice Advisory, a clinical practice guideline that attempts to answer one to three narrow questions. The Practice Advisory methodology is somewhat modified from the full guideline development process to make it easier to complete and publish; some steps are abbreviated but none are skipped. Practice Advisories may be used when only part of an existing guideline needs updating, and more details about practice advisories are provided in the Updates section of this manual.

A full guideline is a more expansive and complete document and may have as many questions as needed. As such, full guidelines involve a more complete methodology, the focus of this manual.

I. Topic Nomination and Approval

The first step in the guideline process is topic nomination. Anyone may nominate a topic. A topic is considered to be formally nominated when the topic nomination form (see Appendix Two) has been completed and emailed to the AES Guidelines and Assessment Committee staff liaison.

Topic nominations must document a search for and summary of existing clinical practice guidelines and note what gaps the new guideline will attempt to fill.

The AES Guidelines and Assessment Committee will evaluate nominations as summarized here and described in more detail in Appendix Three.

Nominations will be scored on a scale of 1 to 7 in three areas:

1. Importance of topic
2. Importance of perceived gap
3. Feasibility

The total score of the three areas is obtained by adding the three numbers together. The initial grading will be performed by two AES Guidelines and Assessment Committee members, and the average of the initial scores from these two reviewers will form the priority score. Any proposals with a priority score of 14 or higher will be added to a ranked list of guideline proposals. If the score is 13 or less, it will be sent back to those who proposed the topic with an option of reworking the topic proposal with an assigned committee member.

A running ranked list of guideline topic proposals that received priority scores, along with results of the proposal evaluations, will be maintained by the AES Guidelines and Assessment Committee and kept on record. The committee makes final decisions about which topic to recommend for development next. There is no guarantee that any guideline will be developed even if it receives a high priority score. Every 2 years, the guideline topic proposal list will be reviewed by the committee. Any topic proposals deemed unlikely to be prioritized for development of a guideline or practice advisory may, at the committee's discretion, be dropped from the list. Those submitting the proposal will be notified if this occurs.

Resource availability for guideline development is at the discretion of the AES Board of Directors and will be monitored by the AES Guidelines and Assessment Committee. If and when guideline development resources are available, the AES Guidelines and Assessment Committee will review the topic proposals list and may choose to accept none, one, or more guidelines the committee deems most important.

With selection of one or more topics, the committee will recommend a preferred document type (practice advisory or full guideline) for each topic. The topic and document type recommendation will be sent for review and approval by the AES Guidelines and Assessment Committee, Council on Clinical Activities, and AES Board of Directors members who do not have relevant conflicts of interest as determined by the AES Professionalism Committee. Approved proposals will then go back to the AES Board of Directors for review and approval. If the AES Board of Directors does not approve a topic, it will be remanded to the AES Guidelines and Assessment Committee.

II. Forming the Work Group

Once a guideline proposal has been approved, the next step is to form the guideline Work Group. Guideline Work Groups will be selected to ensure a variety of perspectives and avoid bias and financial and intellectual conflict. The collective Work Group composition should provide the necessary expertise for both addressing the clinical questions and conducting the technical requirements of guideline development. The size of the Work Group will depend on the topic and complexity of the guideline being developed.

Best efforts will be made to identify appropriate individuals without relevant conflicts of interest. However, it is recognized that this is not always possible in that it may exclude necessary topic experts from participating. For this reason, rigorous management of disclosure of relationships and management of conflict of interest is necessary as outlined in section III of this manual.

The Work Group may include:

- A facilitator (member of the AES Guidelines and Assessment Committee who will keep the guideline on track and report progress to the committee)
- At least two guideline content experts
- Two patients or patient representatives
- A primary care/family practice physician or other physician likely to be impacted by the guideline (if applicable)
- Work Group Lead (generally, but not always, the person who submitted the nomination form)
- A nonconflicted representative nominated from the AAN, American Clinical Neurophysiology Society (ACNS), International League Against Epilepsy (ILAE), or other relevant stakeholders (these are time-limited invitations; note that these representatives must agree to abstain from outside review by their respective organizations to remove any chance of conflict of interest)
- An AES methodologist
- A representative from the AES Board of Directors (if included, the board representative must likewise abstain when the guideline is reviewed by the AES Board of Directors)
- A trainee such as a resident or clinical fellow training in an area relevant to the topic of the guideline

Work Group members may fill up to two roles, so the facilitator might also be one of the experts or possibly the Work Group Lead. The minimum number of people to form a Work Group is five. Gender diversity of the guideline group should be considered.

A methodologist will be approved by the AES Guidelines and Assessment Committee for a specific guideline project. The methodologist must have at least one of the following qualifications:

- Significant experience writing guidelines. Such experience is, at a minimum, first or senior author on five or more guidelines or published systematic reviews. Publications include but are not limited to guidelines developed by the AAN, AES, and systematic reviews published in the Cochrane Database of Systematic Reviews and exclude any guidelines or systematic reviews published either outside a nationally recognized society or under a society without a clearly defined guideline development manual.

- MPH with a minimum of being the first or senior author on three or more guidelines or published systematic reviews (as above)

- PhD in epidemiology or statistics

- Other experience performing the duties of a methodologist to be considered by the AES Guidelines and Assessment Committee and determined on a case-by-case basis

III. Application of AES Conflict of Interest and Copyright Assignment Policy for Guidelines

AES is committed to adhering to policies and procedures designed to ensure production of independent and trustworthy guidelines. To meet this commitment, AES convenes experts for the guideline development process in a manner that minimizes potential influence from industry and other relevant entities. Management and disclosure of guideline developer and reviewer relationships comply with the AES Conflicts of Interest Policies, AES Principles for Industry Relationships, and the *Council of Medical Specialty Societies (CMSS) Code for Interactions with Companies*.[19]

The rigorous processes for disclosure of relationships and management of conflict of interest outlined in this section of the manual are intended to avoid bias and financial and intellectual conflict and to align with the principles outlined in these documents.

A. Disclosure and Determination of Relevance

All relationships must be disclosed. In particular, all relationships with industry must be disclosed, irrespective of perceived relevance to the guideline topic. Per CMSS definition, "industry" includes for-profit entities that develop, produce, market, or distribute drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. However, not all relationships will necessarily create conflict or bias. In addition to complete disclosure regardless of perceived relevancy, prospective Work Group members will also be asked to indicate if they consider a disclosed relationship “relevant” to the guideline topic.

Companies with whom relationships may be a source of relevant conflicts on a particular topic will generally be identified by the AES Guidelines and Assessment Committee in consultation with the AES Professionalism Committee in advance of the start of the guideline project Work Group selection process.

Relationships with non-industry entities (eg, payers, government entities, and not-for-profit organizations) and other types of potential bias also need to be disclosed. Please see subsection D of this section for examples of relationships that impact service on guidelines Work Groups per AES Conflict of Interest policies.

All prospective Work Group members must complete a disclosure form. Information must be disclosed for the Work Group member and for immediate family members (eg, spouse, partner, significant other). Disclosed information will be reviewed by the AES Professionalism Committee with consultation as needed from a representative of the AES Guidelines and Assessment Committee for any relevant relationships that may constitute a conflict of interest. This review will take place before a prospective Work Group member may be officially invited to begin work on the guideline. This disclosure form must be updated at least annually but also at any time if any of the responses are no longer correct and/or current. The AES Professionalism Committee will determine: 1) whether a prospective Work Group member is significantly conflicted (a relationship relevant to the guideline topic), moderately conflicted (a relationship not relevant to the guideline topic), or nonconflicted; and 2) whether a relationship may exclude the individual from participation in all or a portion of the guideline development process.

B. Managing Relationships and Roles

All relationships need to be disclosed. Significant conflicts will be included in the written guideline.

The Work Group Lead or Co-Leads must be free of relevant conflicts, and each must be free of relevant financial conflicts and remain free of such conflicts for at least 1 year following guideline publication. If the Lead or Co-Lead has significant conflicts, another Lead or Co-Lead will be selected.

AES requires that at least two thirds of a guideline Work Group be free of conflicts of interest relevant to the subject matter of the guideline and remain free of such conflicts for at least 1 year following guideline publication. If more than one third of prospective Work Group members have relevant conflicts, the Lead will be contacted to add or change the composition of the group to meet the requirements.

In cases where partnering organizations put forward representatives, these representatives must be considered in the calculation of conflicts of interest. If the organizational representatives have relevant conflicts, the Lead may request a different representative be nominated to meet the requirement of two thirds of members being free of conflict.

If conflicts have not been disclosed and it is determined that such disclosure would have placed a Work Group member in a different category of conflict, the individual may be excluded from the Work Group and/or not allowed to participate in future projects. This will require a majority vote by the AES Professionalism Committee Chair, AES Guidelines and Assessment Committee Chair and Vice-Chair, as well as approval from the AES Board of Directors.

C. Summary of Permitted Relationships by Role in Guideline Development

Table 1 summarizes permitted relationships based on the prospective nominee roles in the guideline Work Group. In all cases, when individuals with relevant conflicts are permitted to participate, there must be a total of at least two thirds working on that step without relevant conflict.

Table 1. Permitted Conflicts of Interest Status for Roles and Steps in the Guideline Development Process

Work Group Member Role	Permitted Conflicts of Interest Status
Work Group Leads and Co-Leads	No relevant conflicts
Proposal writing (drafting questions, defining primary outcomes, setting literature eligibility criteria, conducting preliminary literature search)	All may participate regardless of relevant conflict
Systematic literature search (drafting keywords, reviewing preliminary search results)	All may participate
Abstracts review	No relevant conflicts
Full-text review	No relevant conflicts
Classification of evidence	No relevant conflicts
Writing recommendations	All may participate, but members free of relevant conflict lead the formulation of recommendations, particularly: • Creating final evidence summaries • Rating quality of evidence
Writing draft guideline	All may participate regardless of relevant conflict

Guidelines will be reviewed and approved only by members of the AES Guidelines and Assessment Committee, the AES Council on Clinical Activities, and AES Board of Directors who do not have relevant conflicts of interest as determined by the AES Professionalism Committee.

D. Examples of Relationships That Do or Do Not Impact Service on Guidelines Work Groups

Following are some examples of conflict of interest relationships that have an impact on permitted service in particular roles on a guideline Work Group.

Significant relationships that are relevant to the guideline (relevant conflicts) and **exclude a person completely** from service on a guideline Work Group include:

- Serving as a paid consultant or giving paid lectures for a drug company or device manufacturer relevant to the guideline, including on speaker bureaus

- Owning significant stock in a drug company or device manufacturer relevant to the guidelines (shares greater than $50,000 in value or an equity interest in a privately held company greater than 5%)

- Being a paid employee of a relevant drug manufacturer or device maker

Significant relationships that are relevant to the guideline (Relevant Conflicts) and **do not preclude serving** on a guideline Work Group **but may restrict participation** in certain aspects of the guideline development and require active resolution include:

- Having a relationship that relates to the same or similar topic or issue addressed in the guideline

- Having a relationship with a reasonable possibility of financial, professional, or other personal gain or loss as a result of the guideline content

- Having a relationship with an affected company whereby delivery of care in accordance with the guideline recommendation may have direct regulatory or commercial impact on the company, whether positive or negative

- Engaging to be or serving as an expert witness relevant to the guideline

- Receiving any salary support or other financial remuneration for a clinical trial sponsored from a drug company or device manufacturer relevant to the guideline regardless of whether that compensation is directly to the individual or through their institution

Relationships with industry that are not relevant to the guideline topic and generally will not preclude service in all aspects of the development process (moderately conflicted) but may require active resolution include:

- Conducting or participating in a clinical trial not related to the guideline topic

- Owning shares less than $50,000 in value or equity interest in a privately held company less than 5%

Relationships that are considered nonconflicted and therefore do not preclude participation in on all aspects of the development process include:

- Serving on a data safety monitoring board for a clinical trial for a drug company or device maker, provided that none of the relationships previously described in this subsection D applies

- Receiving salary support from the National Institutes of Health (NIH)

- Providing treatment or diagnostic services to patients which are relevant to the guideline (although Work Group members are requested to disclose the percentage of their practice this represents, so the AES Professionalism Committee may determine if conflict exists)

E. Copyright Assignments

Written copyright assignments from all Work Group members will be a mandatory part of Work Group membership unless copyright cannot be assigned. This ensures the ability to create derivative works, which is a necessary part of implementation. The copyright ownership of AES guidelines resides with the AES unless jointly developed with another society; in this case, a memorandum of understanding will typically specify copyright assignments.

IV. Protocol Development

Work Group members will then write the clinical questions. The questions will be written following the PICO (population, intervention, comparator, outcome) format as shown in Appendix Four. This will be the time for the Work Group members to add, delete, or otherwise modify the PICO questions from the proposal.

Note that the classification of evidence is created with certain specific categories in mind. As such, the questions this manual is designed to address are limited to:

- Therapeutic questions about the efficacy or harm of a specific therapy
- Diagnostic questions about the accuracy of a diagnostic test
- Prognostic questions to determine the relationship between a risk factor and an outcome

Other types of questions are valid and important but beyond the scope of this manual.

When writing a PICO question, it is important to think broadly and consider any possible evidence that may answer the question. For example, if the topic is risk factors for recurrence of single, unprovoked seizures, and Work Group members are aware of several papers about an elevated risk of nighttime seizure recurrence after a single seizure, the question should not be, “Do nocturnal seizures increase the risk of recurrent seizures after a single unprovoked seizure?” Although this question is absolutely correct in that it looks for the evidence we know exists, it does not allow for discovery of evidence of which we are not aware. A more appropriate question that will uncover the evidence not only about nocturnal seizures but also about other risk factors might be, “What are the risk factors for recurrence of single, unprovoked seizures?”

Once the questions are written, the inclusion/exclusion criteria and information sources will be outlined. A preliminary search will be created. Study records including extraction forms, selection process, and data management will be described. All outcomes, including a main outcome for each question and any planned data analysis, will be described. A description of how differences will be reconciled will be included. The methodologist will be available for help with this step.

V. Protocol Approval

Once the protocol has been completed, it is sent to the methodologist for review and approval. If the protocol is not of sufficient methodologic quality, the methodologist may veto the document and return it to the Work Group for revisions. If the protocol is approved by the methodologist, it proceeds to the AES Guidelines and Assessment Committee for consideration. If the committee approves the protocol, it will be sent out for

broad review. Broad review includes public comments and an invitation for review from relevant societies, including the ILAE, AAN, and ACNS.

The Work Group members will then work on responding to these comments. Although a written response is mandatory, there is no explicit requirement for any changes to be made to the document unless the authors deem it necessary.

At this point, any changes to the protocol resulting from input during the broad review are reviewed by the AES Guidelines and Assessment Committee Chair and Vice-Chair, and if considered sufficient, the Work Group is given permission to proceed to the next step.

VI. Systematic Literature Search

At this stage, the Work Group generates a list of keywords and search terms relevant to the proposed guideline. Ideally at least five papers of relevance are found by the Work Group. Papers from previously performed relevant and high-quality systematic reviews should be included. These papers are emailed to the methodologist. One half of these papers and the literature search terms/keywords are given to the librarian who creates the search strategies. The other half of papers are held in reserve and are used to verify the accuracy of the searches.

If Work Group members have access to an institutional librarian for creation of the search, this resource may be tapped. Alternately, the AES will identify a librarian to generate search strategies. When possible, the AES will identify a separate librarian to peer review the preliminary search strategies to ensure they are comprehensive and include articles relevant to the guideline topics. If there are problems with the search, they will be corrected before the search is executed. The preliminary search is typically performed using PubMed.

Once the search has been executed, the methodologist checks and verifies that **all** papers held in reserve are among search results. If relevant articles are missing from the preliminary searches, strategies will be revised to ensure the search is comprehensive. Once all the papers are identified, the search strategies are approved. Once the search strategies are approved, they may be added to the protocol and uploaded to PROSPERO, the National Institute for Health Research international prospective register of systematic reviews.[20]

The literature searches are then executed via PubMed, Embase, and CENTRAL (Cochrane Central Register of Controlled Trials),[21] at a minimum. Other databases may be searched if relevant and feasible. A search of grey literature is required. Grey literature sources may include PROSPERO; DARE (Database of Abstracts of Reviews of Effects)[22] database of quality-assessed systematic reviews of health and social care interventions that may include unpublished data (DARE entries were recorded from 1994 to March 2015 only); ClinicalTrials.gov, a registry and results database of medical interventional studies in human volunteers that may include studies in progress and/or completed but unpublished studies; and/or conference abstracts (search via Embase for some published abstracts or manually via various sources for unpublished abstracts). These are examples and suggestions among many sources of grey literature, and the Work Group may decide on the extent and types of grey literature sources to be searched.

VII. Search Results and Selection of Included Papers

Members of the guideline Work Group with relevant relationships and/or conflicts of interest are not allowed to participate in the rest of this step. This means that they will have a higher bar to reach to qualify for authorship than nonconflicted Work Group members because they will not be able to participate in a significant part of the work.

A. Abstracts Review

Once the searches are completed, abstracts of identified studies are divided up by the methodologist. Abstracts are reviewed independently by two Work Group members who do not have relevant conflicts of interest to identify papers that meet initial eligibility criteria for full-text review. The list of abstracts selected are sent to the methodologist. When the two reviewers disagree on inclusion, they will attempt to reconcile the disagreement collaboratively. If agreed upon a priori by the Work Group and documented in the protocol, a third Work Group reviewer may be invited to review an abstract for which an inclusion decision cannot be reached collaboratively by the two reviewers.

B. Full-Text Review

The methodologist divides and assigns the published studies selected for full text review. Two Work Group members who have no relevant conflicts of interest perform independent reviews of the full-text papers. Unless otherwise specified by the Work Group in the protocol, any studies that are considered to be Class IV evidence (see study classification guidance in Appendix Five, Appendix Six, and Appendix Seven) or any studies that do not answer the PICO questions are culled. **Note:** If the number of studies is relatively small, all studies may be formally classified.

VIII. Classification of Evidence and Using Modified GRADE Process

The methodologist then divides the papers among the Work Group members. Two Work Group members with no relevant conflicts are asked to classify each study by risk of bias (see Appendix Five, Appendix Six, and Appendix Seven). Classification of evidence is based upon the 2015 amendments[2] to the 2011 AAN guidelines manual,[1] with some minor and slightly more conservative changes. At this writing, the AAN process is evolving, so the predication on the 2015 amendments is subject to change.

Following are some notes about classification of evidence:

- Classification of evidence is based on outcome. A study with multiple outcomes may have multiple classifications for different outcomes.

- Loss to Follow-Up – Loss to follow-up in a research study occurs when a subject starts the study but does not complete it. Loss to follow-up is considered in classification of evidence due to potential impact on the estimates of treatment effect on the outcome(s) of interest. The percentage of 83% trial completers is the cutoff for concern for bias among dropouts. This number is concretely chosen based on when the coverage, or percentage of confidence intervals including the true odds ratio, drops below 90%.[23] A commonly used rule of thumb is 80%, but the coverage for including the true odds ratio for 20% loss to follow-up is about 83%, which seems too low. To reach 90% coverage, the loss to follow-up needs to be 14% or less. This choice of at least 83% is clearly a judgment call but is

meant to be a compromise between the conventional 20% loss and the more conservative 14% loss proposed to reach 90% of the true odds ratios in the confidence interval.

A. Review of Classification

Once the papers are classified, the classification is reviewed by the methodologist for accuracy. If there is significant inaccuracy, the methodologist may choose to review all the papers and correct the classification or send it back to the Work Group for a second review. Unless the authors of the guideline have significant experience classifying evidence, it is likely that one or both of these will occur. The final determinant of the classification of a paper is under the purview of the methodologist.

B. Modified GRADE Process

Authors who are considered seriously conflicted do not participate in this step. The process described here is a modification of the GRADE process, described in the GRADE Handbook[24] and GRADE guidelines[25-30] mentioned throughout this document.

Intervention-outcome pairs are then derived from the PICO questions. Intervention-outcome pairs are calculated with 95% confidence intervals. When calculating the confidence interval, if the outcome is a secondary outcome, using the Bonferroni correction is mandatory unless the study in question already corrected for multiple outcomes. If there are more than five secondary outcomes, use the Holm-Bonferroni correction instead. The methodologist will help if there are questions.

When creating a summary effect, if the 95% confidence interval crosses the no effect point, then the summary effect is considered not statistically significant.

The intervention-outcome pairs are reviewed individually, and a strength of evidence is assigned to them, which can be modified up or down based on the GRADE process. Please see Appendix Eight for other details.

If there are outcomes of similar importance, and the results from the GRADE process have different results, use the weakest result.

The end result of the modified GRADE process is an evidence rating for the intervention-outcome pair: high, moderate, low, or very low. The meaning of these ratings is nicely summarized by the World Health Organization in its *WHO Handbook for Guideline Development*.[18] High means that future research is unlikely to change the confidence in the estimate of effect. Moderate means that future research is likely to change the confidence in the estimate of effect and may change the estimate. Low means that future research is very likely to change the confidence in the estimate of effect and is likely to change the estimate. Very low means that the estimate of effect in unknown and/or uncertain.

IX. Writing Draft Recommendations and Vetting via Modified Delphi Process

Work Group members with relevant conflicts of interest are invited back into the active work of the guidelines Work Group. With their help, draft recommendations are written. Each draft recommendation is then vetted through a modified Delphi process.

This process has three steps:

1. Write draft recommendation statements that the Work Group would like to come out of the guideline. The ideal is for the recommendations to be actionable and based on clinically relevant outcomes. At this point, the strength of the recommendations is left open to be determined in later steps.

   Example: In patients with simple partial status epilepticus, an MRI scan [must/should/may] be performed instead of a CT scan of the brain.

2. The recommendation statements need to be justified using evidence-based, as well as nonevidence-based, factors. Most typically, the evidence level will be generated from the GRADE process. This is labeled with "(evid)." The statements can then be further developed by inferences, labeled with "(infer)." Inferences do not come directly from a statement but are inferred from the statement.

   Table 2 shows an example of how inferences might be used: Epilepsy quality indicators in the United States state that head CT imaging is sufficient for patients with epilepsy. Consider a hypothetical situation in which a Work Group wishes to argue that some patients require an MRI scan. There is a high frequency of focal lesions in patients with simple partial status epilepticus (evid). The lesion, or the surrounding tissue, might be the underlying cause of the status epilepticus (infer). An MRI scan is better than a CT scan in detecting brain lesions (evid). Patients with simple partial status epilepticus should have a head MRI scan rather than a CT scan only (infer).

   These inferences are anonymously voted upon by the full Work Group. Votes are sent to the methodologist for tallying and reporting the result. Voting is typically time limited, and lack of response is not counted in the tally.

   Table 2. Inferences Example

"Agree" Votes	Label	Maximum Recommendation Supported
100%	Compelling	A
> 80%-99%	Convincing	B
> 50%-80%	Plausible	C
≤ 50%	Unconvincing	U/R

   In the example, there are two inferences. Each inference is voted upon separately, and the lowest result is taken from multiple inferences for the recommendation. So, if the vote for the first was 100% but the vote for the second was only 75%, the logic of the recommendation would be labeled plausible and could support no higher than a C recommendation.

Note that U and R recommendations are slightly different. U means unknown. R means that the intervention should be used only in a research setting. When a recommendation falls in the U/R category, the Work Group decides whether the recommendation should be a U or an R.

3. The recommendation is now ready for the clinical contextual profile. This is a two-step process. The first step is really a summary of the previous step two. The Confidence in Evidence should be taken from the GRADE table (Table 3).

Table 3. GRADE Clinical Contextual Profiles

Anchor	U/R	C	B	A
Confidence in Evidence	Very Low	Low	Moderate	High
Strength of Inferences	Unconvincing	Plausible	Convincing	Compelling

The lowest of the confidence in evidence and the strength of inferences are used to be the anchor. Continuing with the example in Step 1 at the beginning of this section, the Confidence in Evidence is High and the Strength of the Inference is Plausible.

Table 4. Modified Delphi

Evidentiary Anchor	U/R	C	B	A
Confidence in Evidence	Very Low	Low	Moderate	High
Strength of Inferences	Unconvincing	Plausible	Convincing	Compelling
Recommendation Level	**U/R**	**C**	**B**	**A**
Adherence expected to affect	Few	Some	Most	Nearly all
Variation in patient preferences	Large	Moderate	Small	Minimal
Cost	Prohibitive	Expensive	Moderate	Minimal
Availability	Limited	Some limited availability	Generally available	Universal
Value of benefit relative to harm	Too close to call or harmful	Small	Moderate	Large
Evidentiary anchor	U/R	C	B	A

The Work Group votes on these criteria for the recommendation, typically at the same time as voting on the inferences. Votes are tallied quantitatively, with point assignments as follows:

- U/R = 1 point
- C = 2 points
- B = 3 points
- A = 4 points

The criterion for agreement is that at least 75% of the votes must be either the average rounded down or the average rounded up to the nearest whole number.

Example of vote and tally:

In a vote on cost of performing the MRI scan, one person votes “Prohibitive,” two people vote “Expensive,” and four people vote “Moderate.” The sum of the scores is 17, so the quantitative average is 17 divided by 7 people voting or 2.4, which rounds down to 2 and rounds up to 3.

In this case, we say that consensus is achieved because 6 of 7 votes were either 2 or 3. The value taken for the consensus is the one with the highest number of votes.

Table 5 shows the appearance of the completed corresponding line on the modified Delphi table:

Table 5. Example of Modified Delphi Consensus Results

Recommendation Level	U/R	C	B	A	Consensus Achieved
Cost	Prohibitive	Expensive	Moderate	Minimal	Yes

If consensus is not achieved, Work Group members are allowed to make comments about the issue and another vote is allowed. Up to three votes are allowed to achieve consensus. If consensus is not achieved within three votes, the “Consensus Achieved” column will read “No,” and no recommendation is made.

The recommendation level may be lowered below the evidentiary anchor for any criteria that is lower. The recommendation level can be increased by one level for a value of benefit relative to harm of moderate to large. Level A recommendations can only be achieved if the confidence in the evidence is High.

The resulting recommendation wording is then derived from the recommendation level, as shown in Table 6.

Table 6. Recommendation Language

Recommendation Level	U/R	C	B	A
Wording	There is insufficient evidence or only under the auspices of a research trial	May offer or may inform	Should offer or should inform	Must offer or must inform

Note that recommendations can be created without evidence using this process. In this case, the inferences are voted on as usual, but the a priori assumption is that the evidence is very low. This means that the evidentiary anchor is U/R. Using the modified Delphi process can then allow for the creation of Level C consensus-based recommendations, which have logic and inference but do not have evidence backing them up.

X. Writing the Guideline Draft

In writing the guideline draft, important elements include:

1. Structured abstract and conflicts of interest
2. Introduction, including the objective and definition of the target users of the guideline
3. Questions, which should include the target population of the guideline
4. Methodology, inclusive of how frequently the guideline should be updated
5. Evidence
6. Results of the systematic review (detailing evidentiary anchors after GRADE)
7. Recommendations and clinical context (detailing the explanation for the recommendations and the results of the modified Delphi approach). Different options for management of the condition are to be explicitly discussed here.
8. In the recommendation section, the authors should talk about potential barriers to implementation, as well as potential cost of implementation. If there are links to tools to support implementation, they should be included here, too.
9. Recommendations for future research
10. Disclaimer and acknowledgements
11. Appendices, which must include:
    a. Grading system for classification of articles
    b. Evidence tables that include:
        - Author, year, reference
        - Type of study (eg, therapeutic, prognostic, diagnostic)
        - Classification of evidence
        - Study population (eg, N, mean age, sex, diagnosis)
        - Intervention(s) or tests, as appropriate
        - Outcome measures
        - Results (including confidence intervals when available or calculable)
        - Other (eg, if a study is I/II classification, explain why some outcomes are Class II)
    c. GRADE results for each intervention-outcome pair
    d. Clinical contextual profile from the modified Delphi process

The recommendations may not be altered from those written by the Work Group and agreed upon through the modified Delphi consensus process. The guideline draft must be ready for journal submission and follow the journal requirements.

All AES guidelines will be published in *Epilepsy Currents* unless otherwise specifically approved by the AES Board of Directors. One example of an exception might include copublication of a guideline that is jointly developed with another society.

XI. Guideline Review and Approval Processes

A. AES Guidelines and Assessment Committee Review

The draft guideline is initially reviewed by the methodologist. If the guideline draft does not have sufficient methodologic quality, it can be vetoed by the methodologist. Examples of scenarios that may result in a veto include: significant studies are missing, significant classification of risk of bias inconsistencies remain, or evidence tables are missing. After the draft guideline passes initial review by the methodologist, the AES Guidelines and Assessment Committee carefully reviews the document and votes to agree upon one of three possible responses:

1. No, the document is not ready.
2. Yes, the document is close but needs a few changes before broad review. After incorporation of the changes, the committee votes to see if the document may progress.
3. Yes, the document is ready to move to the next step.

Note that revisions, including significant revisions, should be expected by the Work Group no matter which overall response is given by the committee.

B. Broad Review

The document goes out for broad review to the same organizations selected for the earlier review of the guideline protocol in addition to other organizations identified by the Work Group and AES Guidelines and Assessment Committee. The draft guideline is sent to the Council on Clinical Activities and the AES Board of Directors for their comments, but they are not required at this point to act on it.

C. Journal Review

At this stage, *Epilepsy Currents* (or other journal with approval from the AES Board of Directors) is requested to choose reviewers. The draft will be sent to the reviewers for their anonymous comments with strict time deadlines. While the broad review is happening, the search is updated if it is more than 6 months out of date.

D. Back to the Committee

After the updated literature search and consideration of all the comments, the AES Guidelines and Assessment Committee reviews and again responds as outlined in subsection A in this

section. After responding to committee comments, the Work Group has one last time-limited chance to review the document before submission.

Comments made by the AES Guidelines and Assessment Committee, Council on Clinical Activities, and/or AES Board of Directors as well as journal reviewers are expected to be addressed, with changes made in the guideline. All other comments are to be reviewed and commented upon. If appropriate, changes can be made in the guideline.

E. Journal Review

Congratulations! You are close to being done. *Epilepsy Currents* (or other journal with approval from the AES Board of Directors) peer-reviews the document. If recommendations change due to reviewer concerns, it must be sent back to the AES Guidelines and Assessment Committee for review (subsection D).

F. Review by AES Leadership

Once the draft has received approval from the journal, it is sent to the Council on Clinical Activities and AES Board of Directors for review and final consideration of approval. If there are changes at this point, the document has to be sent back to the journal for review (subsection E). The expected time for AES Board of Directors input that would change recommendations is when they are invited to review the document at broad review. The purpose of this step is for a final check and sign-off before publication.

XII. Implementation and Dissemination

A separate Work Group is formed. This group may include representation from the AES Practice Management Committee and Council on Education to create the implementation tools and consider barriers to implementation, explicitly considering organizational barriers and cost barriers. Once this is complete, at least three tools are created. First, a slide set is created. Then, a summary document is made that details the recommendations. One summary document is made for physicians, and another summary document is made for patients and their families. Other materials may be created so that the message of the guideline can be communicated broadly.

During the implementation period, the guideline and implementation tools are reviewed with the revised AMSTAR (Assessment of Multiple Systematic Reviews)[31] and AGREE II tools[32] to see if there are improvements that would enhance the quality of the next guideline. This review is performed by a methodologist and presented to the AES Guidelines and Assessment Committee. Completed guidelines will be submitted to the National Guideline Clearinghouse and Guidelines International Network or other repository as appropriate and available, unless there is a compelling reason not to do so.

Implementation will include, at a minimum, a slide set for presentation of the information in the guidelines and submission to an appropriate repository.

XIII. Updates

Guideline updates can be a complicated issue. As AES creates more guidelines, the need to update multiple guidelines can create a burden that can slow down or stop the production of new guidelines. This section describes the full guideline update process, along with the process for creation of a Practice Advisory that can help streamline updates.

Review of new evidence occurs every 3 years. The search for new evidence uses the same search strategy(ies) used for the original guideline but with the time filter set to the time after the final search. PubMed is the database searched for a Practice Advisory update, and both PubMed and Embase are searched if a full guideline is updated. An AES Guidelines and Assessment Committee member is assigned to review the abstracts generated by the search and, if necessary, retrieve papers that seem to be relevant.

Papers are graded by the committee member, and any evidence thought to be above Class III or IV is sent to another member for verification.

If there is new evidence that could change recommendations or create new relevant recommendations, the AES Guidelines and Assessment Committee member reports to the committee that the guideline is in need of an update. The committee then votes as to whether the update will be a partial update or a full update. A vote for a partial or full update will require a proposal for approval by the Council on Clinical Activities and the Board of Directors. If there does not appear to be new evidence that would change or create new recommendations, the committee votes to affirm the guideline, and new evidence will be reviewed in three more years.

A full update is one in which the entire process is redone using a full search for new papers. All prior Work Group members should be invited to participate in the Work Group.

In the case of a partial update in which only one or two questions need to be updated, a Practice Advisory will be created. In this case, the Work Group Lead and senior author are invited back into the Work Group. Others may be invited, too.

Updates, whether full or partial, follow the process as outlined previously, with the one exception that the search only needs to include the period after the search of the original review. The exact same literature search, evidence selection, evidence assessment, and evidence synthesis processes detailed in the relevant sections of this manual are performed.

If only a part of a guideline needs updating, the practice advisory may be used as an alternative to a full guideline update. A Practice Advisory answers one to three clinical questions, and its development process abbreviates a few of the elements of the full guideline process. For a Practice Advisory, the Work Group does not need to include patient representatives. Associated societies are not required to be asked for representation. The minimum number of people in the Work Group is three. If there are less than five members of the Work Group when the guideline gets to the modified Delphi process, members of the AES Guidelines and Assessment Committee will be added so there is a minimum of five members. The search does not need peer review. There is no requirement for a grey literature search.

References

1. American Academy of Neurology. *Clinical Practice Guideline Process Manual: 2011 Edition*. St. Paul, MN: American Academy of Neurology; 2011. https://www.aan.com/siteassets/home-page/policy-and-guidelines/guidelines/about-guidelines/11guidelinedevmanual_v408_web.pdf. Accessed February 28, 2020.
2. American Academy of Neurology. *Amendments to the 2011 American Academy of Neurology Clinical Practice Guideline Process Manual*. St. Paul, MN: American Academy of Neurology; 2015. https://www.aan.com/siteassets/home-page/policy-and-guidelines/guidelines/about-guidelines/15processmanualamendment_v607.pdf. Accessed February 28, 2020.
3. Institute of Medicine, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust*. Washington, DC: The National Academies Press; 2011. https://www.ncbi.nlm.nih.gov/books/NBK209539/. Accessed February 28, 2020.
4. Becker M, Neugebauer EA, Eikermann M. Partial updating of clinical practice guidelines often makes more sense than full updating: a systematic review on methods and the development of an updating procedure. *J Clin Epidemiol*. 2014;67(1): 33-45.
5. Brouwers MC, Kho ME, Browman GP, et al; for the AGREE Next Steps Consortium. AGREE II: advancing guideline development reporting, and evaluation in health care. *CMAJ.* 2010;182(18):E839-E842.
6. Council of Medical Specialty Societies. *Principles for the Development of Specialty Society Guidelines*. Chicago, IL: Council of Medical Specialty Societies; 2012. https://cmss.org/wp-content/uploads/2016/02/CMSS-Principles-for-the-Development-of-Specialty-Society-Guidelines-September-20122.pdf. Accessed February 28, 2020.
7. Institute of Medicine, Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: The National Academies Press; 2011. https://www.ncbi.nlm.nih.gov/books/NBK209518/pdf/Bookshelf_NBK209518.pdf. Accessed February 28, 2020.
8. Martínez García L, Arévalo-Rodríguez I, Solà I, et al; for the Updating Guidelines Working Group. Strategies for monitoring and updating clinical practice guidelines: a systematic review. *Implement Sci*. 2012;7:109.
9. Moher D, Shamseer L, Clarke M, et al; and the PRISMA-P Group. Preferred reporting items for systematic reviews and meta-analysis protocols (PRISMA-P): 2015 statement. *Syst Rev*. 2015;4(1):1.
10. Pieper D, Buechter RB, Li L, Prediger B, Eikermann M. Systematic review found AMSTAR, but not R(evised)-AMSTAR, to have good measurement properties. *J Clin Epidemiol*. 2015;68(5):574-583.
11. Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P; for the Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med*. 2012;156(7):525-531.
12. Rosenfeld RM, Shiffman RN, Robertson P. Clinical Practice Guideline Development Manual, Third Edition: a quality-driven approach for translating evidence into action. *Otolaryngol Head Neck Surg*. 2013;148(1 Suppl):S1-S55.
13. Sauro KM, Wiebe S, Perucca E, et al. Developing clinical practice guidelines for epilepsy: a report from the ILAE Epilepsy Guidelines Working Group. *Epilepsia*. 2015;56(12):1859-1869.
14. Scottish Intercollegiate Guidelines Network. *SIGN 50: A Guideline Developer's Handbook*. Edinburgh, Scotland: SIGN; 2015. https://www.sign.ac.uk/assets/sign50_2015.pdf. Accessed February 28, 2020.

15. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;7:10.
16. Turner T, Misso M, Harris C, Green S. Development of evidence-based clinical practice guidelines (CPGs): comparing approaches. *Implement Sci*. 2008;3:45.
17. Vernooij RW Sanabria AJ, Solà I, Alonso-Coello P, Martínez García, et al. Guidance for updating clinical practice guidelines: a systematic review of methodological handbooks. *Implement Sci*. 2014;9:3.
18. World Health Organization. *WHO Handbook for Guideline Development*. World Health Organization; 2010. https://apps.who.int/iris/bitstream/handle/10665/75146/9789241548441_eng.pdf;jsessionid=444FE0BAC54B6C5C94A629D45833135E?sequence=1. Accessed February 28, 2020.
19. Council of Medical Specialty Societies. *Code for Interactions with Companies*. Chicago, IL: Council of Medical Specialty Societies; 2015. https://cmss.org/wp-content/uploads/2016/02/CMSS-Code-for-Interactions-with-Companies-Approved-Revised-Version-4.13.15-with-Annotations.pdf. Accessed August 20, 2020.
20. National Institute for Health Research. PROSPERO: international prospective register or systematic reviews. https://www.crd.york.ac.uk/PROSPERO/. Accessed February 28, 2020.
21. John Wiley & Sons Ltd. Cochrane Central Register of Controlled Trials (CENTRAL). https://www.cochranelibrary.com/central/about-central. Accessed February 28. 2020.
22. Rutgers, the State University of New Jersey. Database of Abstracts of Reviews of Effects (DARE). https://www.libraries.rutgers.edu/indexes/dare. Accessed February 28, 2020.
23. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol*. 2004;19(8):751-760.
24. Schünemann H, Brożek J, Guyatt G, Oxman A; The GRADE Working Group. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. https://gdt.gradepro.org/app/handbook/handbook.html. Updated October 2013. Accessed February 28, 2020.
25. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines 1: introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
26. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines 5: rating the quality of evidence—publication bias. *J Clin Epidemiol*. 2011;64(12):1277-1282.
27. Guyatt GH, Ozman AD, Kunz R, et al. GRADE guidelines 6: rating the quality of evidence—imprecision. *J Clin Epidemiol*. 2011;64(12):1283-1293.
28. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines 7: rating the quality of evidence—inconsistency. *J Clin Epidemiol*. 2011;64(12):1294-1302.
29. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines 8: rating the quality of evidence—indirectness. *J Clin Epidemiol*. 2011;64(12):1303-1310.
30. Guyatt GH, Oxman AD, Sultan S, et al; GRADE Working Group. GRADE guidelines 9: rating up the quality of evidence. *J Clin Epidemiol*. 2011;64(12):1311-1316.
31. Kung J, Chiappelli F, Cajulis OO, et al. From systematic reviews to clinical recommendations for evidence-based health care: validation of Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) for grading of clinical relevance. *Open Dent J*. 2010;4:84-91.
32. Canadian Institutes of Health Research. AGREE Tools. https://www.agreetrust.org/resource-centre/. Accessed July 1, 2020.

Appendices

Appendix One: AES Guideline Development Process

Step One: Nominate and approve topic

Step Two: Form the Work Group

Step Three: Disclose and review potential conflicts of interest

Step Four: Develop the protocol

Step Five: Approve the protocol

Step Six: Find relevant literature

Step Seven: Screen literature search results

Step Eight: Classify evidence and conduct modified GRADE process

Step Nine: Write draft recommendations and vet via modified Delphi process

Step Ten: Write the draft guideline

Step Eleven: Review and approval processes

Step Twelve: Implementation and dissemination

Step Thirteen: Updates

Appendix Two: Guideline Topic Nomination Form

1. Title of Proposed Guideline
2. Specific Aims
    a. Please state the PICO questions to be answered by this guideline. For the PICO questions, what would be a clinically significant outcome? For the PICO questions, what would constitute a large enough outcome to suggest an upgrade when performing the GRADE process?

    b. How much data already exist for this guideline? Are there any relevant systematic reviews that have already been done? If there are, what gaps in knowledge do you hope to address in this guideline that has not already been published?

    c. Based on the best evidence-based medicine of which you are aware, what is your prediction about the results of these PICO questions?
3. Background
        a. Please describe the importance of the topic.

        b. Please describe the amount of practice variation for this topic.

        c. Based on your prediction (1c), how do you think this guideline will impact practice variation?

        d. Other information: Are you aware of any cost data, quality of life data, or high-level related evidence?

        e. Implementation: Do you have any thoughts as to what implementation tools might be useful for this guideline's dissemination, outside of a slide set?
4. Proposed authors (and why you suggest these authors)
5. References

Note: Although there are no prescribed limits on the length of a guideline topic nomination proposal, most are less than five pages.

Appendix Three: Guideline Topic Proposal Evaluation

Guideline topic proposals are evaluated using a scoring system based on three parameters: importance of topic, importance of perceived gap, and feasibility.

Importance of Topic

Scoring: Importance of Topic

1. Unlikely to be used in clinical practice
2. Likely to be useful to some physicians* and patients with epilepsy
3. Likely to be important to some physicians and patients with epilepsy
4. Likely to be useful to a majority of physicians and patients with epilepsy
5. Likely to be important to a majority of physicians and patients with epilepsy
6. Likely to be useful to nearly all physicians and patients with epilepsy
7. Likely to be important to nearly all physicians and patients with epilepsy

   * Physicians who care for patients with epilepsy

Example Evaluation: Importance of Topic

Proposed Topic: A guideline on recommendations for intraoperative management of patients with epilepsy.

Although many patients will undergo surgery at some time, not every patient does, so it could not apply to "nearly all" patients.

It is probably true that a majority of physicians would find this guideline useful. Some would find it very useful and might consider it important. It is similarly true that a majority of patients would probably have an operation of some nature during some time in their life.

Thus, this proposed guideline would score a 4.5 for importance of topic (somewhere between useful and important to a majority of physicians and patients with epilepsy).

Importance of Perceived Gap

Scoring: Importance of Perceived Gap

1. Uniform practice
2. Some variance of practice
3. Significant variance of practice and/or the evidence are considered not well known

4. Some variation of practice, and there are data to show that some practice may not follow established evidence and/or guidelines

5. There is significant variation of practice, and there are data to show that some practice may not follow established evidence and/or guidelines

Example Evaluation: Importance of Perceived Gap

Proposed Topic: A proposed guideline on epilepsy surgery referral

We know from several papers that referrals happen very late with patients with epilepsy, but some people follow the guideline closely. This would suggest that this proposed guideline would score a 5 in the area of perceived gap.

Feasibility (minimum of 0)

Scoring: Feasibility

These three components are added together:

1. Facility of answering the question (0 to 2)
    - 2 points for being able to be answered in a practice advisory
    - 1 point for being able to be answered in a clinical practice guideline
    - 0 points for likely being a multiguideline project
2. Surrogate outcomes (-2 to 2)
    - 2 points if the outcomes are primary (eg, myocardial infarction, risk of fracture)
    - 0 points if the outcomes are secondary (eg, coronary calcification, bone density)
    - -2 points if the outcomes are tertiary (eg, calcium-phosphorus product)
3. Clinical query (1 to 3)
    - 3 points for clinical query yielding < 200 studies
    - 2 points for clinical query yielding < 500 studies
    - 1 point for clinical query yielding < 1000 studies

Example Evaluation: Feasibility

Proposed topic/clinical query: Guideline is about guidance for antidepressants and epilepsy

PubMed Clinical Queries interface (search results are limited to specific clinical research areas, as opposed to unfiltered PubMed which provides a more comprehensive search) is found at: http://www.ncbi.nlm.nih.gov/pubmed/clinical

Clinical Study Category: Therapy
Scope: Broad
[Note: The above settings are usually preset in the PubMed Clinical Queries interface.]

Type in the search bar: epilepsy AND antidepressants

Press the "Search" button.

Results: Assume the search yielded 1431 clinical studies. This proposed guideline would receive a 0 for feasibility.

Example of Complete Topic Proposal Scoring:

Returning to the example topic, "intraoperative management of patients with epilepsy," this complete topic proposal scoring example assumes the champion for the guideline submitting the topic proposal has not previously written guidelines.

Proposed Topic: A guideline on recommendations for intraoperative management of patients with epilepsy

Importance of topic: 4.5
Importance of perceived gap: 5
Feasibility: 5

Total: 14.5

Appendix Four: PICO Questions

The proposed clinical questions comprise a key part of the topic nomination form, and the PICO format should be used to frame and write answerable questions.

P = Population

I = Intervention

C = Comparator

O = Outcome

T = Timing (optional)

S = Setting (optional)

PICO questions may fall into one of three general categories:

1. Therapeutic – Efficacy or harm of an intervention
2. Diagnostic –Accuracy of a diagnostic test
3. Prognostic – Outcomes or risk factors for a disease, condition, or injury

PICO questions for each category should be written according to the corresponding guidance and examples that follow.

Example Therapeutic Question: Efficacy of an Intervention

For patients with medically refractory epilepsy, does having a rescue medication prescription compared with not having a rescue medication prescription have an impact on frequency of emergency room visits for uncontrolled seizures?

Population = patients with medically refractory epilepsy
Intervention = rescue medication prescription
Comparator = no rescue medication prescription
Outcome = frequency of emergency room visits for uncontrolled seizures

Additionally, a PICO question may include Time for outcome. For example, for epilepsy surgery, the question might state that an outcome must be measured for at least 6 months. Another optional addition to a PICO question is Setting; for example, outpatient or inpatient settings.

The PICO question above is in the format for a therapeutic question. For other types of questions, the PICO format is altered to fit the type of question.

For diagnostic test questions, the comparison is either another test known to diagnose the problem or a reference standard. A reference standard is the gold standard or definitive diagnostic test for the condition.

Example Diagnostic Question: Accuracy of a Diagnostic Test

- *For patients with a single seizure, is a CT scan of the head without contrast as effective as an MRI scan of the brain in detecting significant brain abnormalities?*

Prognostic questions follow a similar format but without the cointervention.

Example Prognostic Question: Outcomes or risk factors for a disease, condition, or injury

- *For patients with a single seizure, does the result of an MRI scan of the brain predict the risk of recurrence?*

These two entities, diagnostic questions and prognostic questions, are considered together because the classification of bias is measured in similar ways.

Appendix Five: Classification of Evidence – Therapeutic Interventions

Class I

- Randomized, controlled clinical trial (RCT) in a representative population
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups or there is appropriate statistical adjustment for differences

- Also required:
    a) Concealed allocation
    b) Primary outcome(s) clearly given and no more than two outcomes are named as primary
    c) Outcome was prespecified before the trial began
    d) Exclusion/inclusion criteria clearly defined
    e) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias*

- Additional criteria apply only to two special trial types (noninferiority/equivalence or crossover trials). If the trial is not one of these special types, ignore these criteria.

    f) For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following criteria are also required:
        1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
        2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (eg, for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
        3. The inclusion and exclusion criteria for patient selection and the outcomes of patients receiving the standard treatment are comparable with those of previous studies establishing efficacy of the standard treatment
        4. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

    g) For crossover trials, these criteria are also required:
        1. There must be a comparison of baseline characteristics of groups A-B vs B-A demonstrating substantial equivalence or statistical adjustments for their differences (if present). This takes the place of the baseline characteristics criteria noted above
        2. Both period and crossover effects must be examined statistically, with adjustments if significant effects are present

Class II

- An RCT lacking one or two criteria among a) through f) under Class I requirements. Note that f) is not considered lacking if the trial is not a noninferiority or equivalence trial

- A cohort trial meeting all criteria a) through f). Note that f is not considered lacking if the trial is not a noninferiority or equivalence trial
- A noninferiority of equivalence trial meeting criteria f) 1-3.
- A crossover trial meeting one of criteria g) under Class I requirements, as long as it meets all the other criteria for the type of trial it is
- Masked or objective outcome assessment
- Relevant baseline characteristics are presented and substantially equivalent between treatment groups or there is appropriate statistical adjustment for differences (unless it is a crossover trial, then follow the rules for a crossover trial)

Class III

- Controlled studies (including well-defined history controls or patients serving as their own controls)
- There is a description of major confounding differences between groups which that could affect outcome
- Outcome assessment is masked, objective, or performed by someone who is not member of the treatment team
- Evidence of selective reporting: a priori outcome specified in the protocol which was either failed to be reported or not reported in enough detail to be included in a meta-analysis

Class IV

- Did not include patients with the disease
- Did not include patients receiving different interventions
- Undefined or unaccepted interventions or outcome measures
- No measures of effectiveness or statistical precision were presented or calculable

***** For binary outcomes, please use 17% dropouts (loss to follow-up) as the cutoff. You may, as an option, look at the loss to follow-up, assign these patients to the worst-case scenarios, and see if the results would change.[a] For nonbinary outcomes, please use a 17% loss to follow-up as the cutoff.

[a] Dettori JR. Loss to follow-up. *Evid Based Spine Care J*. 2011; 2(1):7-10.

Appendix Six: Classification of Evidence – Diagnostic Accuracy

Class I

- Prospective cohort
- Broad spectrum of patients suspected of having the disease
- Disease status is unknown before the study begins or the disease status determination is made without knowledge of the diagnostic study result
- Also required:
    a) Inclusion criteria defined
    b) The number of the subjects enrolled in the study must have both the diagnostic test and disease status measured to have a minimal potential for bias.
    * Subjects are considered enrolled if they sign the consent, regardless of whether they are eventually included in determining the outcome

Class II

- A retrospective cohort or case-control study meeting criteria a) and b) under Class I requirements
- Includes a broad spectrum of persons with and without the disease
- The diagnostic test result and the disease status are objective or determined without knowledge of one another

Class III

- A cohort or case-control study not meeting both criteria a) and b) under Class I requirements
- Includes a narrow spectrum of persons with or without the disease
- The diagnostic test result and the disease status are objective, determined without knowledge of one another, or performed by different investigators

Class IV

- Did not include patients suspected of having the disease
- Did not include patients with and without the disease
- Undefined or unaccepted independent reference standard
- No measures of diagnostic accuracy or statistical precision presented or calculable

* For binary outcomes, please use 17% dropouts (loss to follow-up) as the cutoff. You may, as an option, look at the loss to follow-up, assign these patients to the worst-case scenarios, and see if the results would change.[a] For nonbinary outcomes, please use a 17% loss to follow-up as the cutoff.

[a] Dettori JR. Loss to follow-up. *Evid Based Spine Care J*. 2011; 2(1):7-10.

Appendix Seven: Classification of Evidence – Prognostic Accuracy

Class I

- Prospective cohort
- Broad spectrum of patients at risk for developing the outcome
- Outcome measurement is objective or determined without knowledge of risk factor status
- Also required:
    a) Inclusion criteria defined
    b) A number of the subjects enrolled in the study must have both the risk factor and outcome measured to minimize bias.
    * Subjects are considered enrolled if they sign the consent, regardless of whether they are eventually included in determining the outcome

Class II

- A retrospective cohort or case-control study meeting criteria a) and b) under Class I requirements
- Includes a broad spectrum of persons with and without the risk factor and outcome
- The presence of the risk factor and outcome are determined objectively or determined without knowledge of one another

Class III

- A cohort or case-control study not meeting both criteria a) and b) under Class I requirements
- Includes a narrow spectrum of persons with or without the risk factor
- The presence of the risk factor and the outcome are objective, determined without knowledge of one another, or performed by different investigators

Class IV

- Did not include patients suspected of the disease
- Did not include patients with and without the disease
- Undefined or unaccepted independent reference standard
- No measures of diagnostic accuracy or statistical precision presented or calculable

* For binary outcomes, please use 17% dropouts (loss to follow up) as the cutoff. You may, as an option, look at the loss to follow-up, assign these patients to the worst-case scenarios, and see if the results would change.[a] For nonbinary outcomes, please use a 17% loss to follow-up as the cutoff.

[a] Dettori JR. Loss to follow-up. *Evid Based Spine Care J*. 2011; 2(1):7-10.

Appendix Eight: GRADE Process

A. Steps in the GRADE Process

1. The intervention-outcome pair has the outcomes combined in a meta-analysis unless there are specific reasons why such a meta-analysis would be misleading
2. The data is *initially* anchored at:
    - **High** if there are two or more congruent Class I studies
    - **Moderate** if there is one Class I study or two or more congruent Class II studies
    - **Low** if there is one Class III study or two or more Class III studies
    - **Very Low** if there is one Class III study or no studies above Class IV
3. The papers are then reviewed using the GRADE criteria (There is a series of articles explaining the GRADE process; see Guyatt 2011, GRADE guidelines 1.)

    There are five major criteria that can result in downgrades: Limitations, Inconsistency, Indirectness, Imprecision, and Publication bias. There are also reasons for upgrades.

B. Reasons for Downgrades

1. **Limitations** is taken care of by the I to IV classification system, which rates the risk of bias of the study.

2. **Inconsistency** (see Guyatt 2011, GRADE guidelines 7): Downgrade if there are important unexplained inconsistencies between the highest-class studies.

    A very common reason to explain the apparent inconsistency in study results is the lack of statistical precision of the studies.

    Examples of reasons why one might consider downgrading:
    - Widely varying point estimates without a clear understanding of why they are different
    - Nonoverlapping confidence intervals without a clear understanding of why they are different
    - If a meta-analysis is done, an i^2 value of 75% or higher (generally documenting a substantial to considerable heterogeneity)

3. **Indirectness** (see Guyatt 2011, GRADE guidelines 8): Downgrade if there are important limitations in the generalizability of the evidence due to the patient population included, inclusion criteria, intervention used, or outcome measured. For example, surrogate outcomes might be a reason for a downgrade. According to the GRADE methodology, very indirect evidence can be downgraded by two levels. Another common reason for a downgrade would be the intervention that cannot be routinely implemented due to the sophistication or rigor seen in the trial that showed its efficacy.

    Do not downgrade intervention-outcome pairs for population indirectness with studies that were already downgraded for being narrow spectrum.

4. **Imprecision** (see Guyatt 2011, GRADE guidelines 6): Rate down if the 95% confidence intervals between treatment and effect include different clinical outcomes. Optimal information size can also be used to consider whether to rate down.

5. **Publication Bias** (see Guyatt 2011, GRADE guidelines 5): If there are at least five studies, please do a funnel plot. Downgrade when there appears to be publication bias in the plot. There are other ways to measure this, but the funnel plot is recommended.

B. Reasons for Upgrades (see Guyatt 2011, GRADE guidelines 9)

There are three basic categories for upgrade:

- If there is a two-fold or more increase or reduction in risk, this is considered a large effect. In this case, upgrade.
- If there is a five-fold or more increase or reduction in risk, this is considered for a double upgrade. The double upgrade is nominal and can be used to counteract a downgrade.
- The presence of a dose-response curve is a possible reason for upgrading.

Another possible reason for upgrading is when residual confounders would result in an underestimate of a treatment effect. Residual confounding occurs when there is imperfect measurement of covariates. This can lead to unexpected or unexplained results. An example of this occurs in a study by Chen and colleagues[a] when the point estimate for smoking during pregnancy appears to be protective when mothers are split into only two groups by age. A more careful examination looking at exact maternal age shows a no-effect point estimate. If the residual confounding would suggest a negative effect and the study shows a positive effect, suggesting an underestimate of treatment effect, the study can be upgraded.

C. Applying Upgrades and Downgrades

In general, downgrades typically downgrade the anchor one level, although it is possible to downgrade the anchor by multiple levels. Upgrade(s) can only upgrade the anchor by a single level. The effect of a combination of upgrades and downgrades is at the discretion of the Work Group but there can be no upgrades by more than one level. This is a modification of the GRADE criteria, which allows for multiple upgrades. This modification of the GRADE methodology is, in part, due to the fact that upgrades are already explicitly allowed in the Delphi part of the methodology.

[a] Chen CL Gilbert TJ, Daling JR. Maternal smoking and down syndrome: the confounding effect of maternal age. *Am J Epidemiol*. 1999;149(5):442-446.